Pharmacology for Nurses

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Chapter 4
Pharmacokinetics

Pharmacology

- The study of drugs and their interactions with living systems.

- It is divided into Pharmacodynamics (PD) (actions of drug on the body) and Pharmacokinetics (PK) (actions of the body on the drug).

Pharmacokinetics (PK)

- It is the study of drug movement throughout the body, drug metabolism and drug excretion.

- **Basic PK processes:**

1. Absorption: The movement of a drug from its site of administration into the blood.
2. Distribution: The movement of a drug throughout the body.
3. Metabolism: (Biotransformation) The enzymatic alteration of drug structure.
4. Excretion: The removal of a drug (and its metabolite) from the body.

Absorption

- It is the movement of a drug from its site of administration into the blood.
- **Factors affecting drug absorption:**

1. Rate of dissolution: drug must be dissolved before absorbed. Rapid dissolution = rapid absorption = rapid onset of action
2. Surface area: The larger the surface area available for absorption the faster the absorption. (Stomach vs. small intestine).
3. Blood flow: drugs are absorbed rapidly from sites were blood flow is high (drug-free blood rapidly replacing blood containing newly absorbed drug).

Absorption

- **Factors affecting drug absorption:**

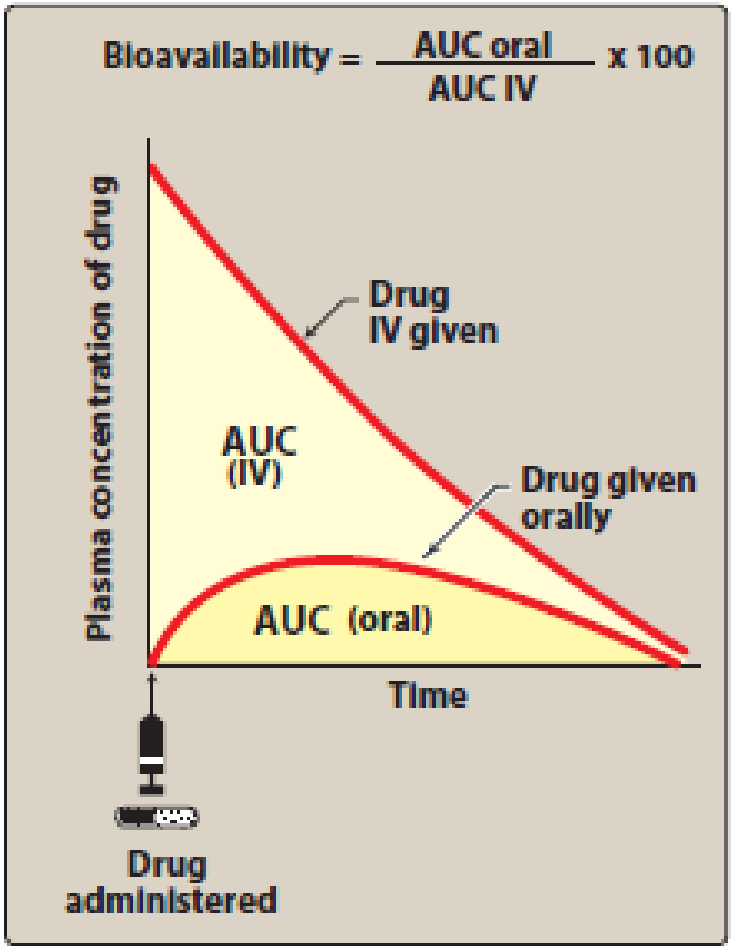
4. Lipid solubility: highly lipid-soluble drugs are absorbed more rapidly – readily cross membranes.

5. pH partitioning (ion trapping): Absorption will be enhanced if the difference between the pH of plasma and the pH of the site of administration (greater tendency of drug to be ionized in the plasma)

Absorption

- **Bioavailability**: It is the rate and extent to which an administered drug reaches the systemic circulation.

- For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%.



Routes of Drug Administration

- **Routes of drug administration:**

1. Enteral (by mouth): Oral (PO) and sublingual/buccal
2. Parenteral (by injection): intravenous (IV), Intramuscular (IM) and Subcutaneous (subQ)
3. Others: Oral and nasal inhalation, intrathecal/intraventricular, transdermal, topical, rectal

Routes of Drug Administration

- **Routes of drug administration:**

- Pharmaceutical preparations for oral administration:

1. **Tablets**: active ingredient(s) plus excipients being compressed together.
2. **Enteric-coated formulations**: to protect drugs from stomach acid / to protect the stomach drugs that cause gastric discomfort
3. **Sustained-release preparations**: formulation dissolves slowly – drug is released steadily throughout the day.

Distribution

- It is the movement of a drug throughout the body.
- Phases of distribution:

a) Blood flow to tissues
b) Exiting the vascular system
c) Entering cells

- The distribution of a drug depends on blood flow (brain, liver, kidneys vs. skeletal muscles, adipose tissue), capillary permeability (liver vs. brain capillaries-BBB), binding of drugs to plasma proteins (plasma albumin – always remain in blood stream) and entering the cells (transport system and/or lipid solubility).

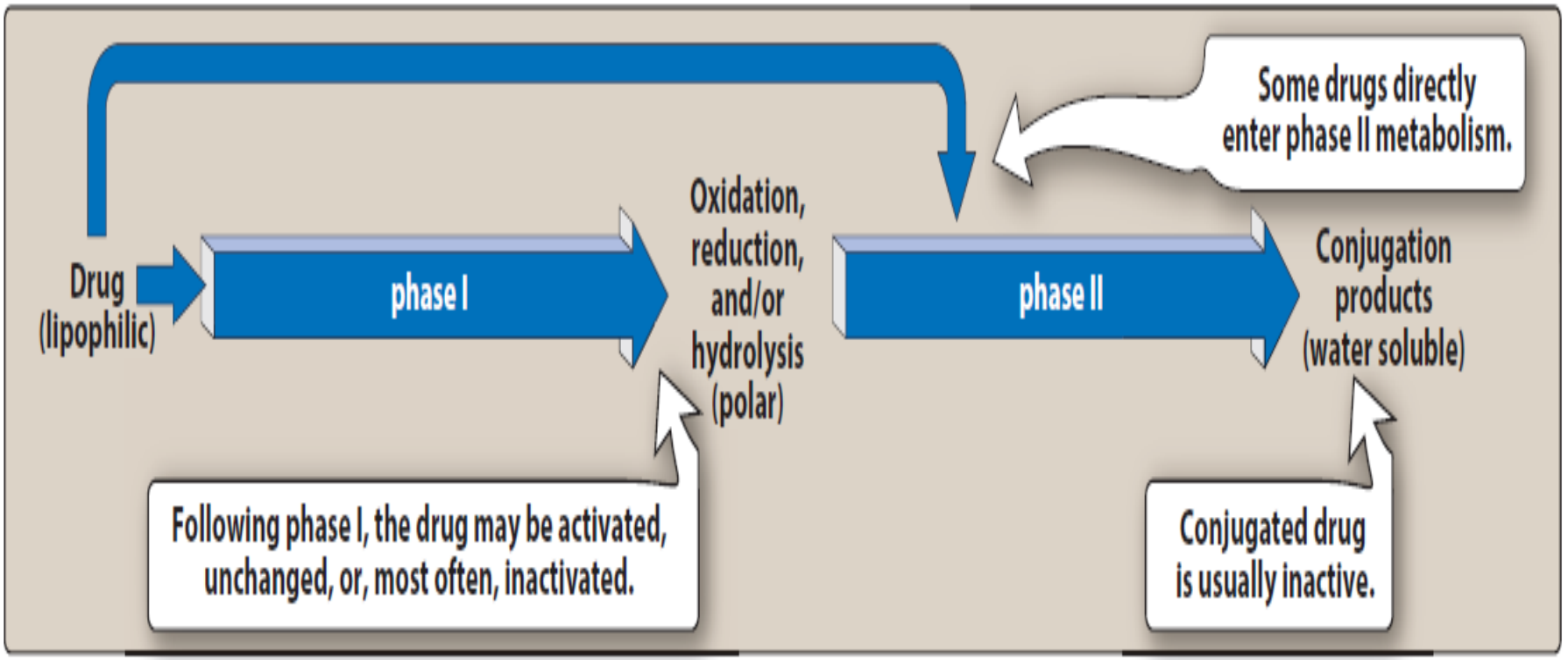
Metabolism

- Also called biotransformation.
- It is the enzymatic alteration of drug structure.
- Lipid soluble drugs must be sufficiently polar (water-soluble) to be eliminated from the body (e.g. via kidneys).
- The major site of drug metabolism is the liver – mostly carried out by hepatic microsomal enzyme system (P450 system – cytochrome P450). (Phase I and Phase II metabolism)

Metabolism

- **Therapeutic consequences of drug metabolism:**

1. Accelerated renal excretion of drugs
2. Drug inactivation
3. Increase therapeutic action
4. Activation of prodrugs
5. Increased or decreased toxicity

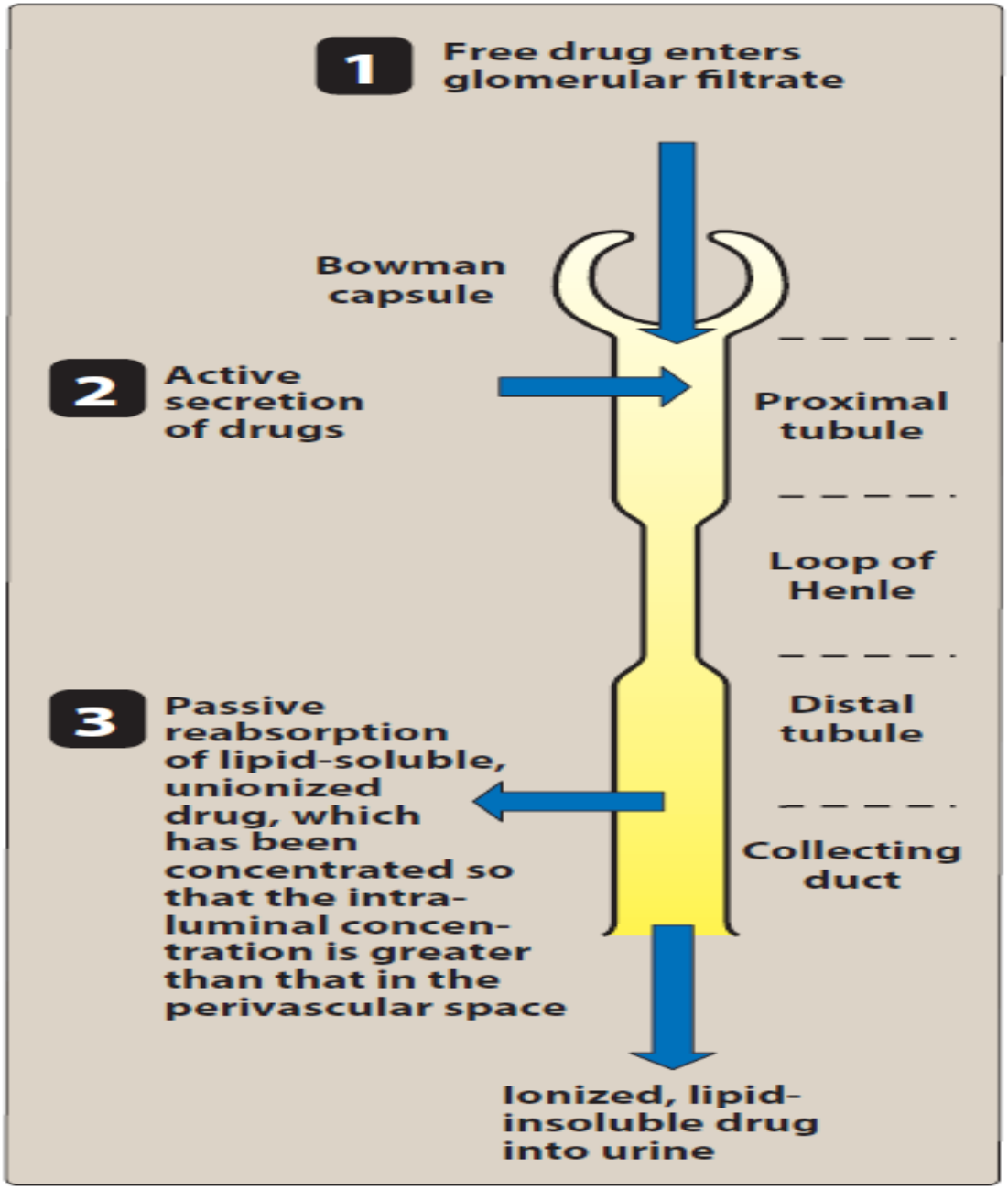

Some drugs directly enter phase II metabolism.
Drug (lipophilic)
phase I
Oxidation, reduction, and/or hydrolysis (polar)
phase II
Conjugation products (water soluble)
Following phase I, the drug may be activated, unchanged, or, most often, inactivated.
Conjugated drug is usually inactive.

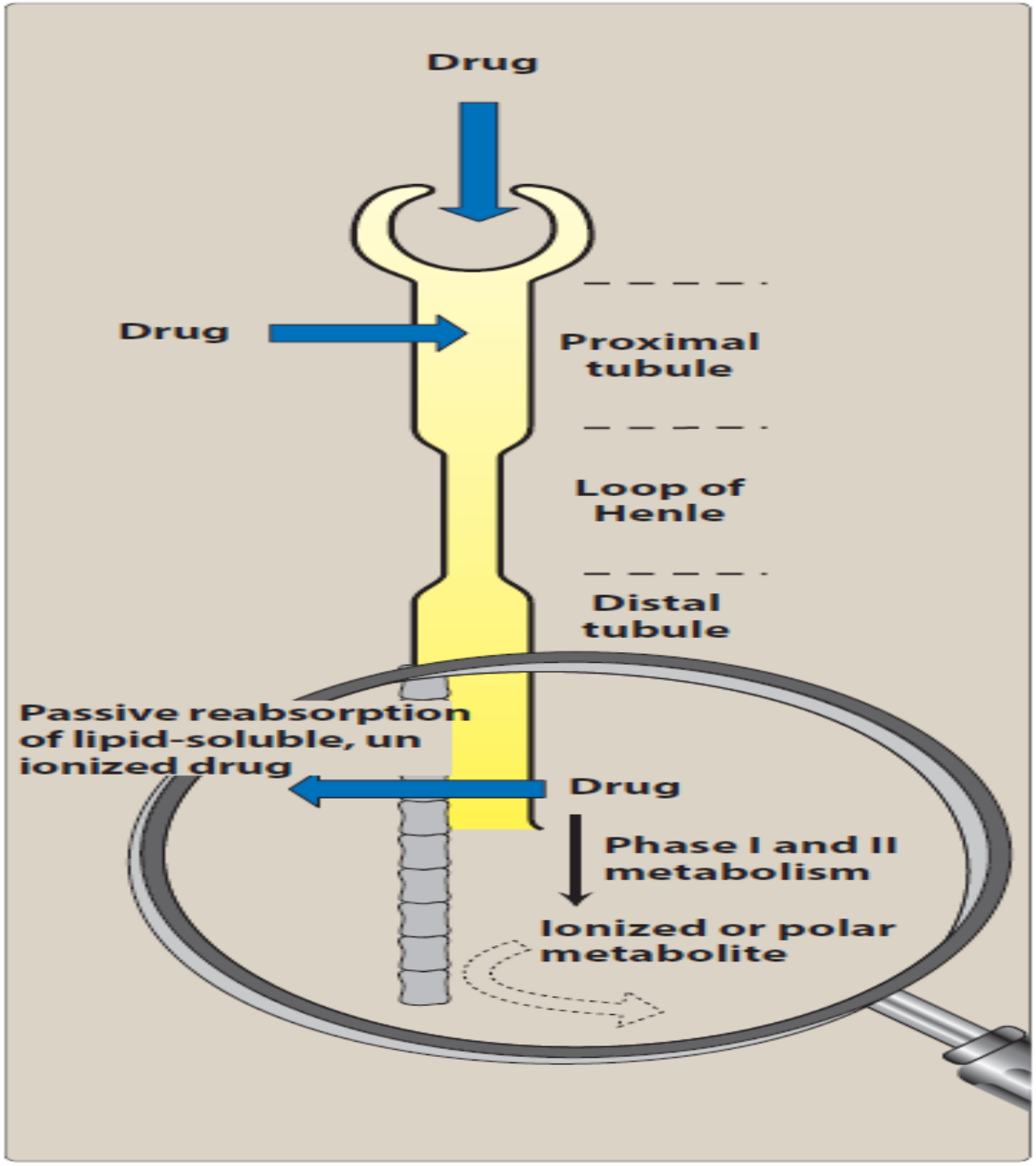
Excretion

- It is the removal of drugs and/or their metabolites from the body.

- **Routes of excretion:**

1. Kidneys / the most important organ for drug excretion (in urine)
2. Breast milk
3. In bile (excreted in feces)
4. Lungs (volatile anesthetics) (expired air)
5. Sweat and saliva


1
Free drug enters glomerular filtrate
Bowman capsule
2
Active secretion of drugs
Proximal tubule
Loop of Henle
3
Passive reabsorption of lipid-soluble, unionized drug, which has been concentrated so that the intra-luminal concen-tration is greater than that in the perivascular space
Distal tubule
Collecting duct
Ionized, lipid-insoluble drug into urine


Drug
Drug
Proximal tubule
Loop of Henle
Distal tubule
Passive reabsorption of lipid-soluble, un ionized drug
Drug
Phase I and II metabolism
Ionized or polar metabolite

Plasma Drug Levels

- Plasma drug levels are monitored to regulate drug responses.

- Important terms:
- **Minimum effective concentration (MEC)**: the plasma drug level below which therapeutic effects will not occur.
- **Toxic concentration**: the plasma level at which toxic effects begin.
- **Therapeutic range**: range of plasma drug levels falling between the MEC and the toxic concentration.
- **Drug half-life ($t_{1/2}$)**: the time required for the amount of drug in the body to decrease by 50%. Half-life of a drug determines the dosing interval.

Chapter 5
Pharmacodynamics

Pharmacology

- The study of drugs and their interactions with living systems.

- It is divided into Pharmacodynamics (PD) (actions of drug on the body) and Pharmacokinetics (PK) (actions of the body on the drug).

Pharmacodynamics (PD)

- The study of the biochemical and physiologic effects of drugs and the molecular mechanisms by which those effects ae produced.

- It is the study of what drugs do to the body and how they do it.

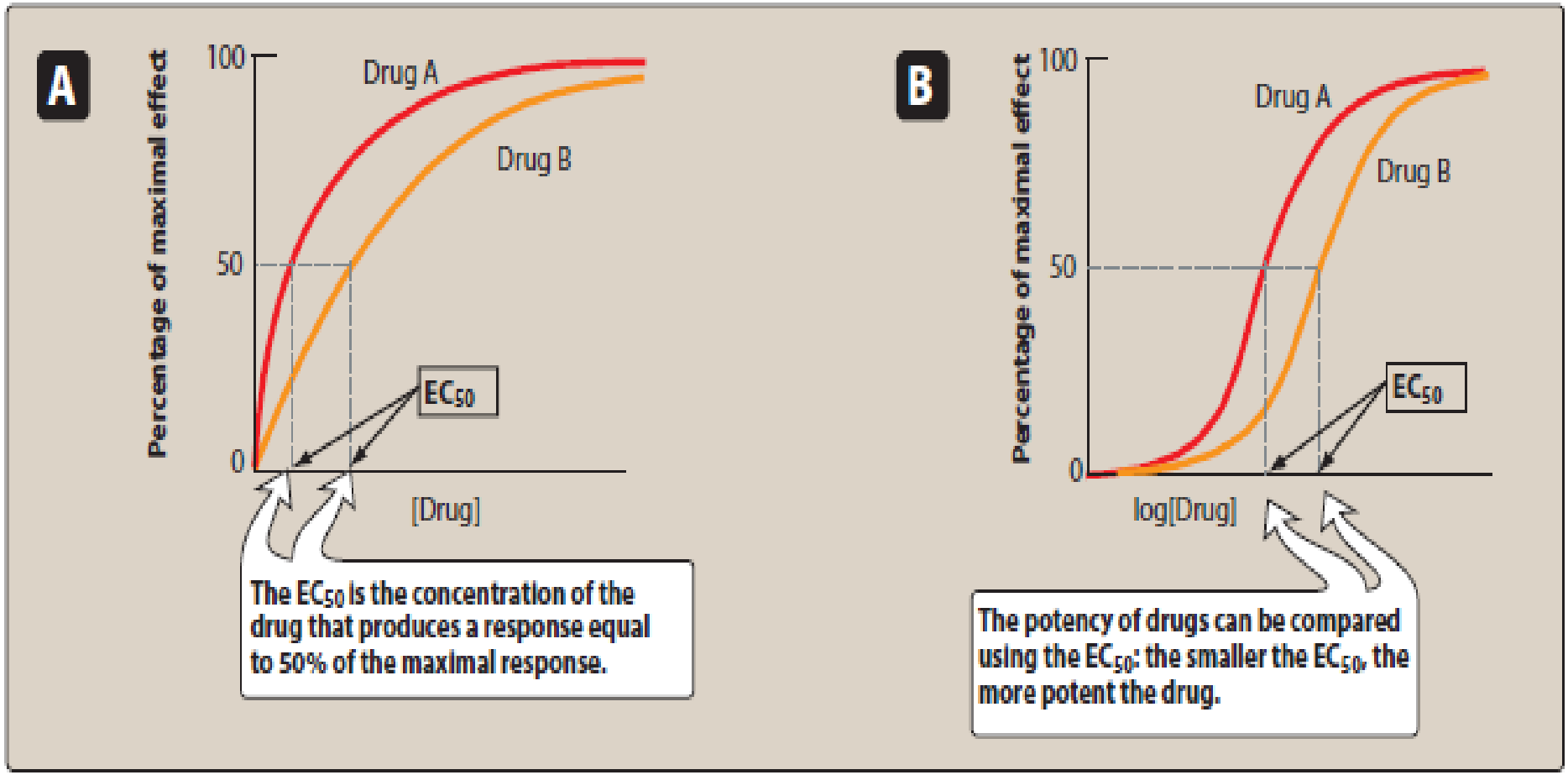
Dose-Response Relationship

- The relationship between the size of an administered dose and the intensity of the response produced.

- It is presented using dose-response curves.

- **Dose-response curves reveal two characteristics properties of drugs:**

1. Maximal efficacy (E_{max})
2. Relative potency

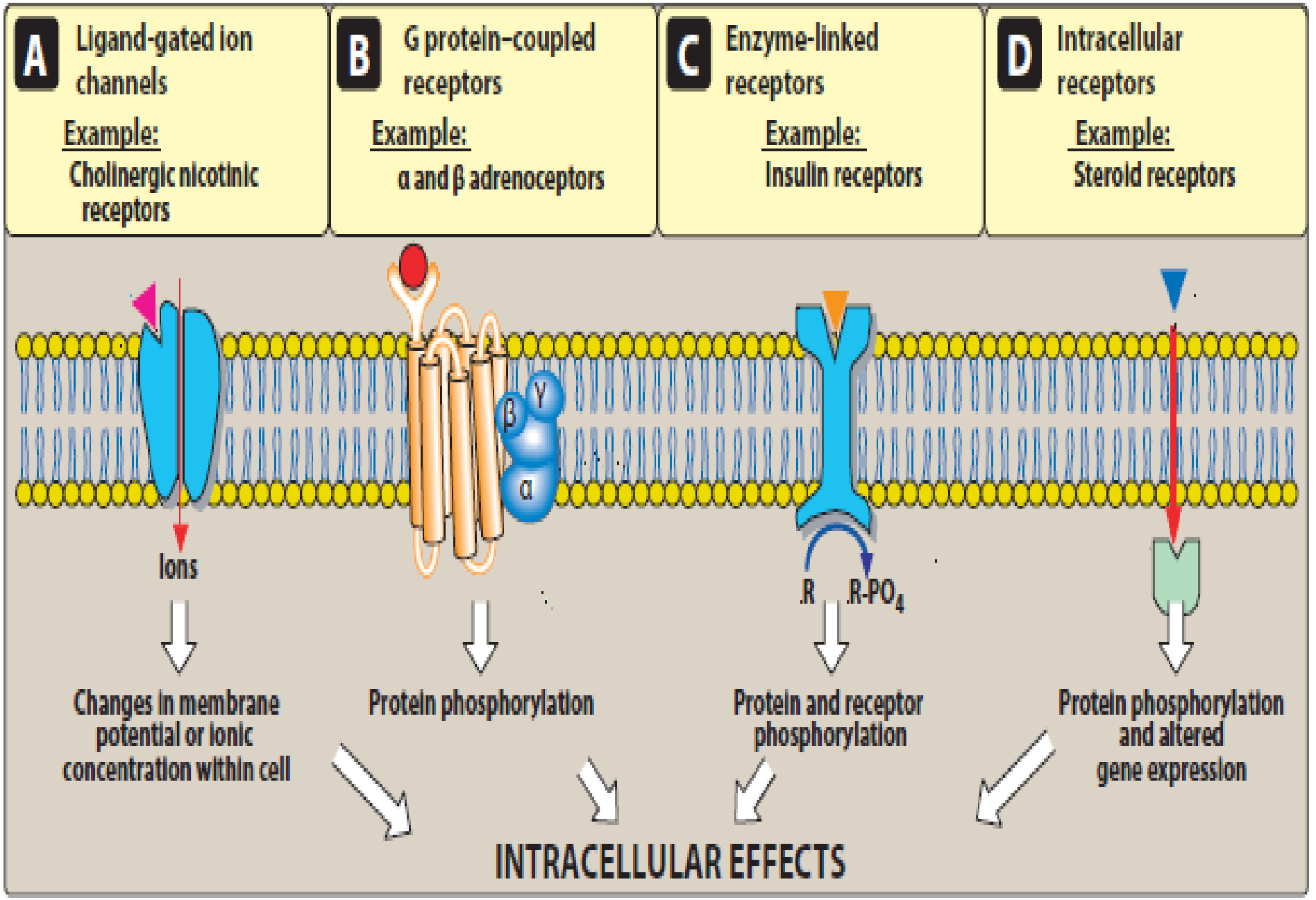

A
Percentage of maximal effect
100
50
0
Drug A
Drug B
EC50
[Drug]
The EC50 is the concentration of the drug that produces a response equal to 50% of the maximal response.
B
Percentage of maximal effect
100
50
0
Drug A
Drug B
EC50
log[Drug]
The potency of drugs can be compared using the EC50: the smaller the EC50, the more potent the drug.

Receptors

- Receptors are macromolecules in the body that drug interact with to produce its effects.

- **The four primary receptor families:**

1. Ligand-gated ion channels (transmembrane receptors)
2. G-protein coupled receptor systems (transmembrane receptors)
3. Enzyme-linked receptors (transmembrane receptors)
4. Intracellular receptors


A
Ligand-gated ion channels
Example:
Cholinergic nicotinic receptors
B
G protein–coupled receptors
Example:
α and β adrenoceptors
C
Enzyme-linked receptors
Example:
Insulin receptors
D
Intracellular receptors
Example:
Steroid receptors
Ions
β
γ
α
R
R-PO4
Changes in membrane potential or ionic concentration within cell
Protein phosphorylation
Protein and receptor phosphorylation
Protein phosphorylation and altered gene expression
INTRACELLULAR EFFECTS

Agonists, Antagonist, and Partial Agonists

- **When drugs bind to receptors, they can:**

1. Mimic the action of endogenous regulatory molecules / activate receptors – called **Agonists**

2. Block the action of endogenous regulatory molecules / prevent receptor activation – called **Antagonists**

3. Mimic the action of endogenous regulatory molecules (activate receptors), but produces a response with less intensity than agonists – called **Partial Agonists**

Agonists, Antagonist, and Partial Agonists

- **Types of Antagonists:**

1. **Noncompetitive Antagonists:**

- They bind to the receptors irreversibly.

2. **Competitive Antagonists:**

- They bind to the receptors reversibly.
- Their effect can be reversed with high concentrations of agonists.

❖ **Drug responses that do not involve receptors:**

- Antacids, antiseptics, laxatives, and chelating agents.

Therapeutic Index (TI) of a Drug

- It is a measure of drug safety.
- It is the ratio of a drug's LD_{50} (average lethal dose) to its ED_{50} (average effective dose).
- Larger (high) value indicate a wide margin between doses that are safe and toxic (e.g. penicillin). Drug relatively safe.
- Smaller (low) value – need to be cautious (e.g. warfarin). Drug is relatively unsafe.

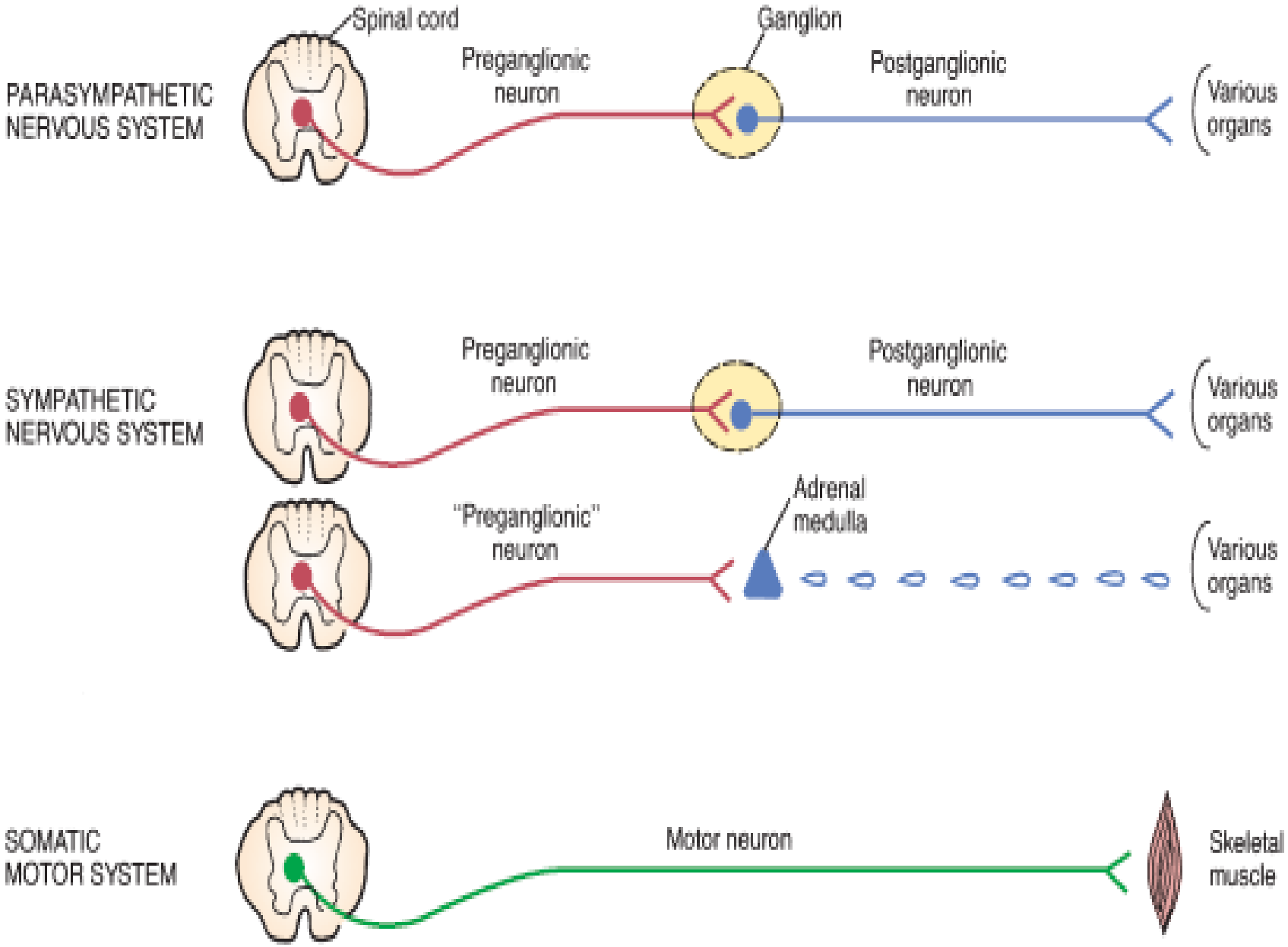
Chapter 13
Physiology of the Peripheral Nervous System

Nervous System

- **The nervous system has two main divisions:**

1. The Central Nervous System
2. The Peripheral Nervous System: composed of two major subdivisions:
    a) The Somatic Motor System
    b) The Autonomic Nervous System

- **Autonomic Nervous System is further subdivided into:**
    a) The Parasympathetic Nervous System
    b) The Sympathetic Nervous System

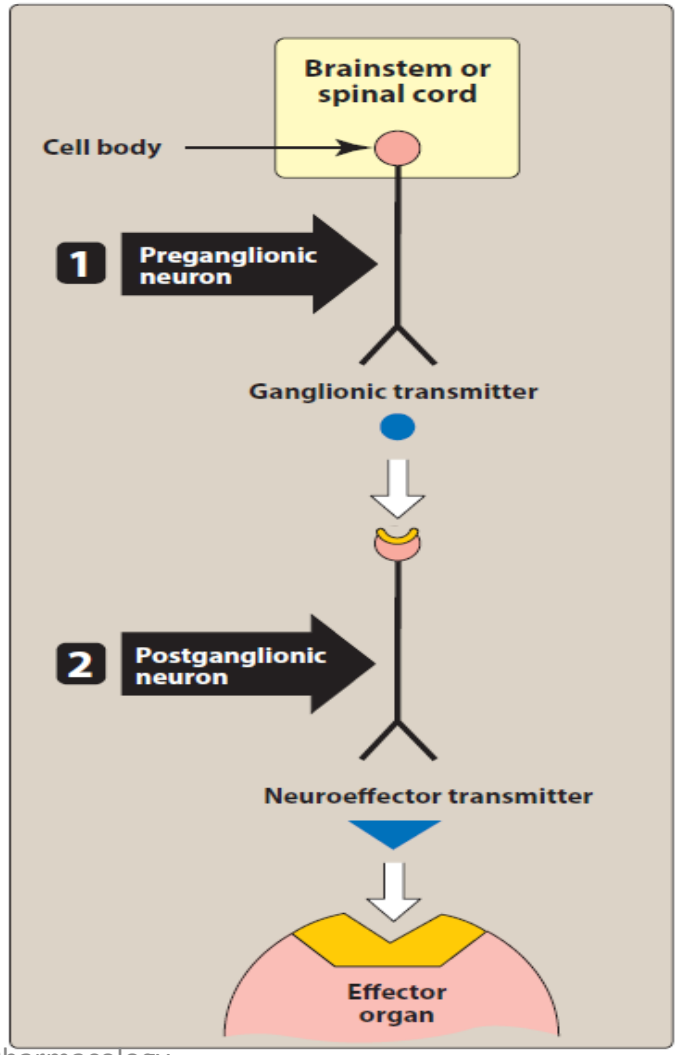

PARASYMPATHETIC NERVOUS SYSTEM
Spinal cord
Preganglionic neuron
Ganglion
Postganglionic neuron
Various organs
SYMPATHETIC NERVOUS SYSTEM
Preganglionic neuron
Postganglionic neuron
Various organs
"Preganglionic" neuron
Adrenal medulla
Various organs
SOMATIC MOTOR SYSTEM
Motor neuron
Skeletal muscle

Somatic Motor System

- Motor division
- It is under voluntary control
- Contraction of the skeletal muscles
- The site of action for drugs affecting somatic motor system is the neuromuscular junction.

Autonomic Nervous System

- Motor division
- It is involuntary
- Carry nerve impulses from the spinal cord to effector organs by two types of efferent neurons: preganglionic and postganglionic neurons
- Involvement of ganglia



Autonomic Nervous System

- **Functions of the parasympathetic nervous system:**

1. Slowing heart rate (reduce cardiac work; conserve energy)
2. Increasing gastric secretions (digestion)
3. Emptying the bladder (excretion of waste)
4. Emptying the bowl (excretion of waste)
5. Focusing the eye for near vision
6. Constricting the pupil (miosis)
7. Contracting bronchial smooth muscles

- Does not discharge as a complete system
- “Rest-and-digest”

Autonomic Nervous System

- **Functions of the sympathetic nervous system:**

1. Regulating the cardiovascular system:

   heart – increases cardiac output

   vasoconstriction of arterioles and veins

   vasoconstriction/vasodilation by epinephrine from adrenal medulla

   (By that: maintain blood flow to brain, redistribution of blood during exercise, compensation for blood loss by causing vasoconstriction)

Autonomic Nervous System

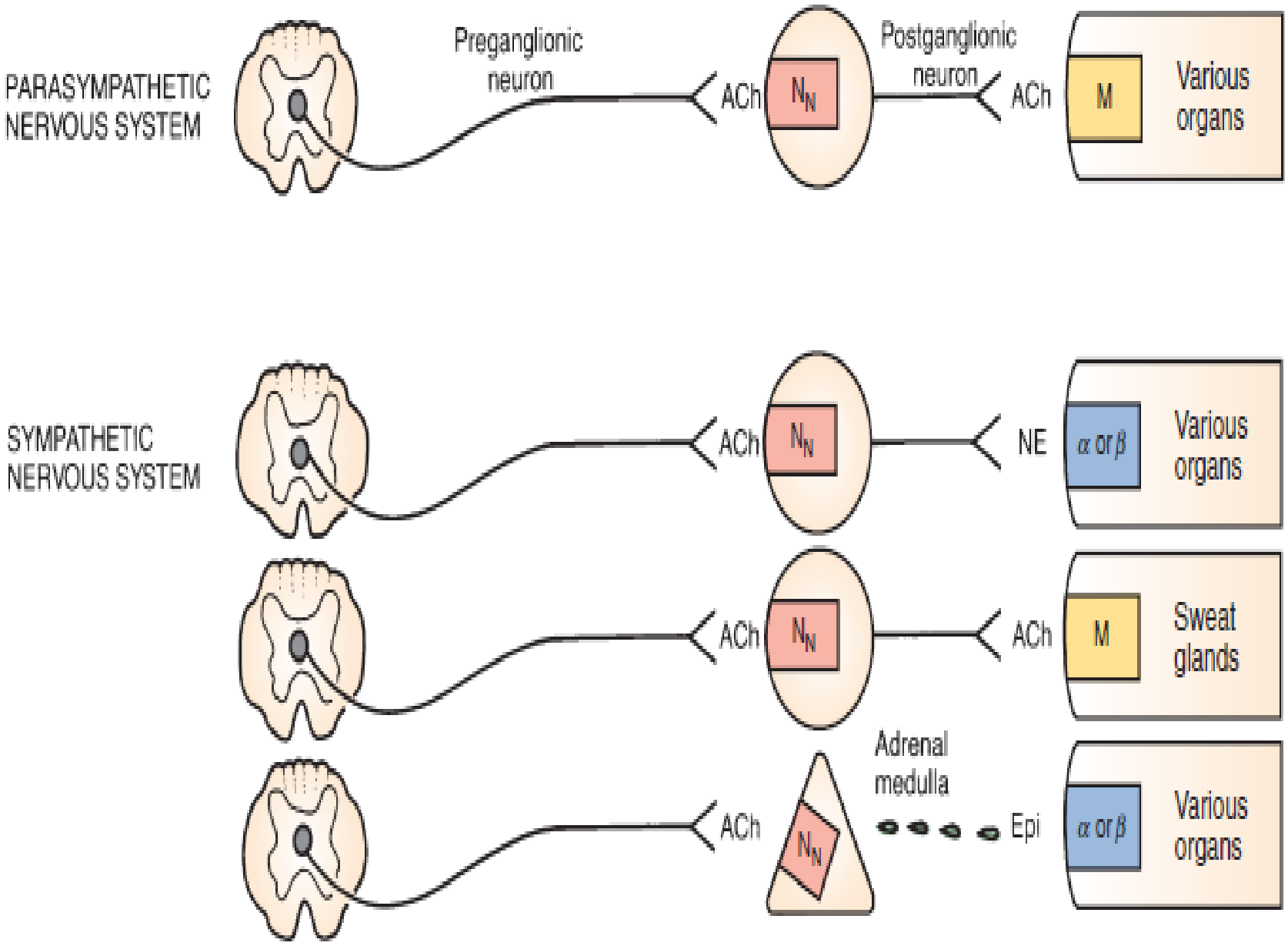
- **Functions of the sympathetic nervous system:**

2. Regulating body temperature:

    Regulating blood flow to skin

3. Implementing the “fight-or-flight” reaction

    Increasing heart rate / dilating bronchi / dilating pupils / mobilizing stored energy / shunting blood away from skin and viscera into skeletal muscles


PARASYMPATHETIC
NERVOUS SYSTEM
Preganglionic
neuron
ACh
N_N
Postganglionic
neuron
ACh
M
Various
organs
SYMPATHETIC
NERVOUS SYSTEM
ACh
N_N
NE
α or β
Various
organs
ACh
N_N
ACh
M
Sweat
glands
Adrenal
medulla
ACh
N_N
Epi
α or β
Various
organs

- **Sweat glands:**
  - Sympathetic Nervous System
  - Involvement of preganglionic and postganglionic neurons
  - Acetylcholine neurotransmitter from both neurons
  - Receptors: nicotinic receptor – ganglia / muscarinic receptor – sweat glands

Peripheral Nervous System

- **Neurotransmitters involved in the Peripheral Nervous System:**

1. Acetylcholine (ACh)
2. Norepinephrine (NE)
3. Epinephrine (Epi)

Peripheral Nervous System

- **Receptors involved in the Peripheral Nervous System:**

1. **Cholinergic receptors (cholinoceptors):**

- Receptors that mediate responses to ACh
- Subdivided into: nicotinicN (N_N), nicotinicM (N_M), and muscarinic

2. **Adrenergic receptors (adrenoceptors):**

- Receptors that mediate responses to NE and Epi
- Subdivided into: alpha1 (α_1), alpha2 (α_2), beta1 (β_1), and beta2 (β_2)
- Dopamine receptor: respond to dopamine / those of clinical significance – vasculature of kidneys – dilates red blood vessels – enhancing renal perfusion

Cholinergic Agonists

Chapter 14: Muscarinic Agonists and Antagonists

Chapter 15: Cholinesterase Inhibitors and Their Use in Myasthenia Gravis

Cholinergic Agonists

- **Direct-acting cholinergic agonists:**
- Mimic the effects of ACh by binding directly to cholinoceptors (muscarinic or nicotinic) – receptor activation

- Muscarinic agonists – parasympathomimetic agents

- All of the direct-acting cholinergic drugs have a longer duration of action than ACh.

- **Muscarinic Agonists:**

  Bethanechol, Cevimeline, Pilocarpine

Direct-Acting Cholinergic Agonists

Bethanechol:

Preadministration Assessment:

- Therapeutic Goal: Nonobstructive urinary retention

- Identifying high-risk patients: Contraindicated for patients with peptic ulcer, urinary tract obstruction, intestinal obstruction, hypotension, asthma

Implementation: Administration:

- Route: PO

- Administration:

  Reduce gastric upset – 1hr before meals or 2hs after

  Bedpan or bathroom need to be readily accessible

Direct-Acting Cholinergic Agonists

Bethanechol:

Ongoing Evaluation and Interventions:

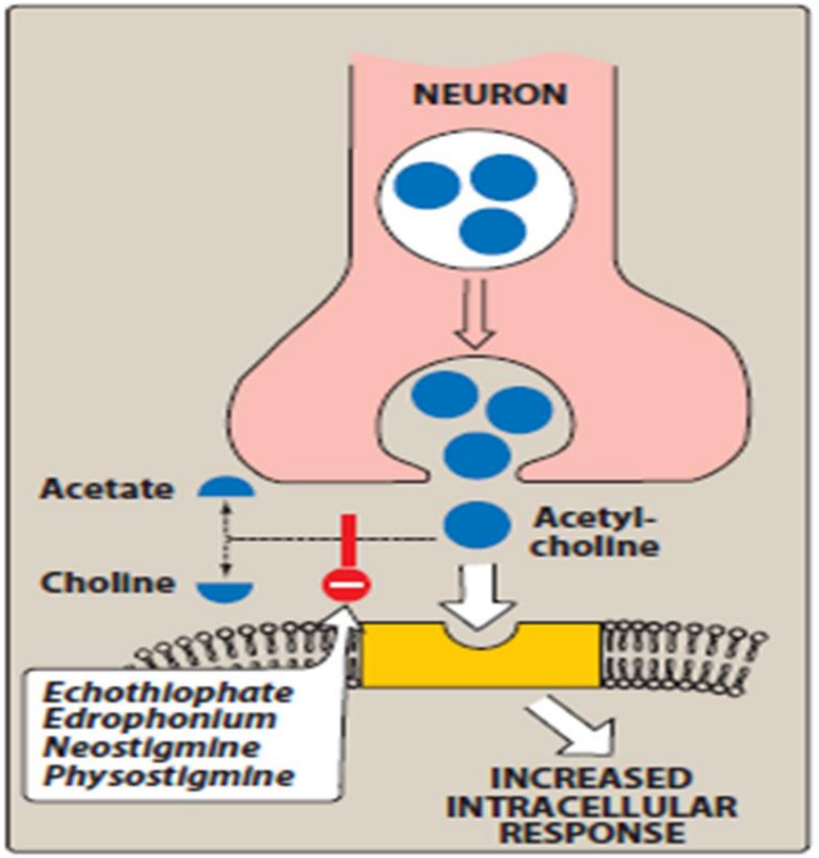
- Evaluating Therapeutic Effects: Monitor fluid intake and output

- Minimizing Adverse Effects: Inform patients about manifestations of muscarinic excess and advise them to notify the prescriber if they occur (salivation, *sweating*, involuntary urination and defecation, bradycardia, severe hypotension)

- Management of Acute Toxicity: Parenteral Atropine (muscarinic antagonist)

Cholinergic Agonists

- **Indirect-acting cholinergic agonists:**
- Cholinesterase (ChE) is an enzyme that specifically cleaves ACh to acetic acid and choline and, thus, terminates its actions.
- ChE inhibitors inhibit ChE at all cholinergic
- Reversible ChE inhibitors and irreversible ChE inhibitors.



Indirect-Acting Cholinergic Agonists

- **Reversible ChE inhibitors:**
  - Neostigmine, Pyridostigmine, Physostigmine, Donepezil

- **Irreversible ChE inhibitors:**
  - Echothiophate

Indirect-Acting Cholinergic Agonists

Preadministration Assessment:

- Therapeutic Goal:
  - Neostigmine (PO, IM, IV, subQ) / Pyridostigmine (PO, IV) = treatment of Myasthenia gravis + reversal of nondepolarizing neuromuscular blockade (from pancuronium)
  - Physostigmine (IM, IV) = antidote to poisoning by muscarinic antagonists
  - Donepezil (PO) = Alzheimer's disease
  - Echothioplate (topical) = Glaucoma

- Identifying high-risk patients: Contraindicated for patients with mechanical obstruction of the intestine or urinary tract

Indirect-Acting Cholinergic Agonists

Implementation: Administration:

Administration:

- Myasthenia Gravis:

  Assess the patient's ability to swallow – if impaired – parenteral medication

  Optimize dose – distinguish between insufficient vs. excessive dosing

- Reversing nondepolarizing neuromuscular blockade:
  Administer drug + support respiration until muscle strength has recovered fully

- Treating muscarinic antagonist poisoning:
  Physostigmine by IM or slow IV injection

Indirect-Acting Cholinergic Agonists

Implementation: Measures to Enhance Therapeutic Effects:

Myasthenia Gravis :

- Promoting compliance: Inform patients that MG is not usually curable – treatment lifelong – take medication as prescribed

Ongoing Evaluation and Interventions:

Evaluating Therapeutic Effects:

- Myasthenia Gravis: Monitor and record times of drug administration, fatigue occurs, muscle strength and ability to swallow, and signs of muscarinic stimulation.

- Monitor for *myasthenic crisis* – respiratory support + increased dose

Indirect-Acting Cholinergic Agonists

Ongoing Evaluation and Interventions:

Minimizing Adverse Effects:

- Excessive muscarinic stimulation: Inform patients about manifestations of muscarinic excess and advise them to notify the prescriber if they occur – Management with atropine

- Cholinergic crisis: skeletal muscle paralysis + excessive muscarinic stimulation – Management with mechanical ventilation and atropine

Cholinergic Antagonists

Chapter 14: Muscarinic Agonists and Antagonists

Chapter 16: Drugs That Block Nicotinic Cholinergic Transmission: Neuromuscular Blocking Agents

Muscarinic Antagonists

- They do not block nicotinic receptors; no action on NMJ and autonomic ganglia
- Block the actions of ACh on muscarinic receptors – parasympatholytic agents
- Block muscarinic receptors of sweat glands
- **Muscarinic Antagonists:**

  Atropine, Ipratropium Bromide, oxybutynin, cyclopentolate

Muscarinic Antagonists

Preadministration Assessment:

- Therapeutic Goal:
  - Atropine (PO, IM, IV, subQ) = preanesthetic medication and treatment of bradycardia, biliary colic, intestinal hypertonicity and hypermotility, and *muscarinic agonist poisoning*
  - Ipratropium Bromide (inhalation) = treatment of asthma, COPD, and rhinitis caused by allergies or the common cold
  - Oxybutynin (PO) = Treatment of overactive bladder
  - Cyclopentolate (opthalmic solution) = to produce mydriasis and cycloplegia in ophthalmic procedures

- Identifying high-risk patients: Contraindicated in patients with glaucoma, intestinal atony, urinary tract obstruction, tachycardia, use with caution in patients with asthma

Muscarinic Antagonists

Implementation: Administration:

- Administration: Dry mouth from muscarinic blockade may interfere with swallowing – moisten the mouth

Ongoing Evaluation and Interventions:

- Minimizing Adverse Effects:
  - Xerostomia: Teach patients that xerostomia can be relieved by chewing gum, sucking on hard candy, and sipping fluids
  - Blurred vision: Avoid hazardous activity if vision is impaired
  - Photophobia: Advise patients to wear sunglasses outdoors
  - Urinary retention: Advise patients to void just before taking anticholinergic medication – catheterization or bethanechol may be required if urinary retention is severe

Muscarinic Antagonists

Ongoing Evaluation and Interventions:

- Minimizing Adverse Effects:
  - Constipation: Advise patients to increase dietary fiber and fluids intake laxative may be needed if constipation is severe
  - Hyperthermia: Advise patients to avoid vigorous exercise in warm environments
  - Tachycardia: Monitoring

- Minimizing Adverse Interactions:
  - Antihistamines, tricyclic antidepressants, and phenothiazines have antimuscarinic effects – with atropine or other anticholinergics cause excessive muscarinic blockade.
  - Resembles psychosis and psychotic episodes – need to be differentiated to give proper medication

Muscarinic Antagonists

Ongoing Evaluation and Interventions:

- Management of Acute Toxicity:
  - Limit absorption – giving activated charcoal
  - Administer physostigmine

Neuromuscular Blocking Agents

- These drugs block cholinergic transmission between motor nerve endings and the nicotinicM receptors. (Muscle relaxant)

- They act as antagonists (nondepolarizing) or agonists (depolarizing) at the nicotinicM receptors on the endplate of the NMJ

- Therapeutic uses: muscle relaxation during surgery / facilitation of mechanical ventilation / endotracheal intubation / diagnosis of myasthenia gravis / adjunct to electroshock therapy.

- **Neuromuscular Blocking Agents:**

  Pancuronium, Vecuronium, Rocuronium, Atracurium, Cisatracurium, Succinylcholine (the only depolarizing agent)

Neuromuscular Blocking Agents

Preadministration Assessment:

- Therapeutic Goal:

  As above

- Identifying high-risk patients:
  - All neuromuscular blockers are used with caution in patients with myasthenia gravis.
  - *Succinylcholine* is contraindicated in patients with low pseudocholinesterase activity, a personal or familial history of malignant hyperthermia, or conditions that predispose to hyperkalemia (major burns, multiple trauma, denervation of skeletal muscle, upper motor neuron injury)

Neuromuscular Blocking Agents

Implementation: Administration:

- Routes:

  IV: All neuromuscular blockers

  IM: Only succinylcholine

- Administration: Administered by skilled clinicians – neuromuscular blockers are dangerous

Implementation: Measures to Enhance Therapeutic Effects:

- Neuromuscular blockers have no effect on perception of pain – adequate anesthesia must be accompanied during surgeries.
- Prolonged paralysis during mechanical ventilation – care should be taken to ensure comfort (e.g. positioning the patient comfortably, moistening the mouth periodically).
- Patients may be awake (but won't appear to be – they can hear – paralyzed) – conversations held in their presence should convey only information appropriate for them to hear

Neuromuscular Blocking Agents

Ongoing Evaluation and Interventions:

- Minimizing Adverse Effects:
  - Apnea:
    - All neuromuscular blockers can cause respiratory arrest. Facilities for intubation and mechanical ventilation should be immediately available.
    - Monitor every 17 minutes at least when drug is discontinued
    - To reverse respiratory blocker – ChE inhibitor can be used (for nondepolarizing agents only)
  - Hypotension:
    - Secondary to ganglionic blockade – antihistamines may help to counteract this effect
  - Patients with malignant hyperthermia or conditions predisposing to hyperkalemia – *Succinylcholine is contraindicated*
  - Muscle pain may be caused by succinylcholine – not unusual

Neuromuscular Blocking Agents

Ongoing Evaluation and Interventions:

- Minimizing Adverse Interactions:
  - Antibiotics:
    - Aminoglycosides and tetracyclines can intensify neuromuscular blockade – use them with caution
  - ChE inhibitors:
    - Contraindicated with *succinylcholine*

Ganglionic Blocker

- **Mecamylamine:**
- Competes with ACh for binding to nicotinicN receptors in autonomic ganglia – blocks transmission at all autonomic ganglia

- Blocks sympathetic effects on sweat glands, arterioles and veins (predominant sympathetic tone)

- Blocks parasympathetic effects on salivary glands, ciliary muscles, iris sphincter, urinary bladder, GI tract, heart (predominant parasympathetic tone)

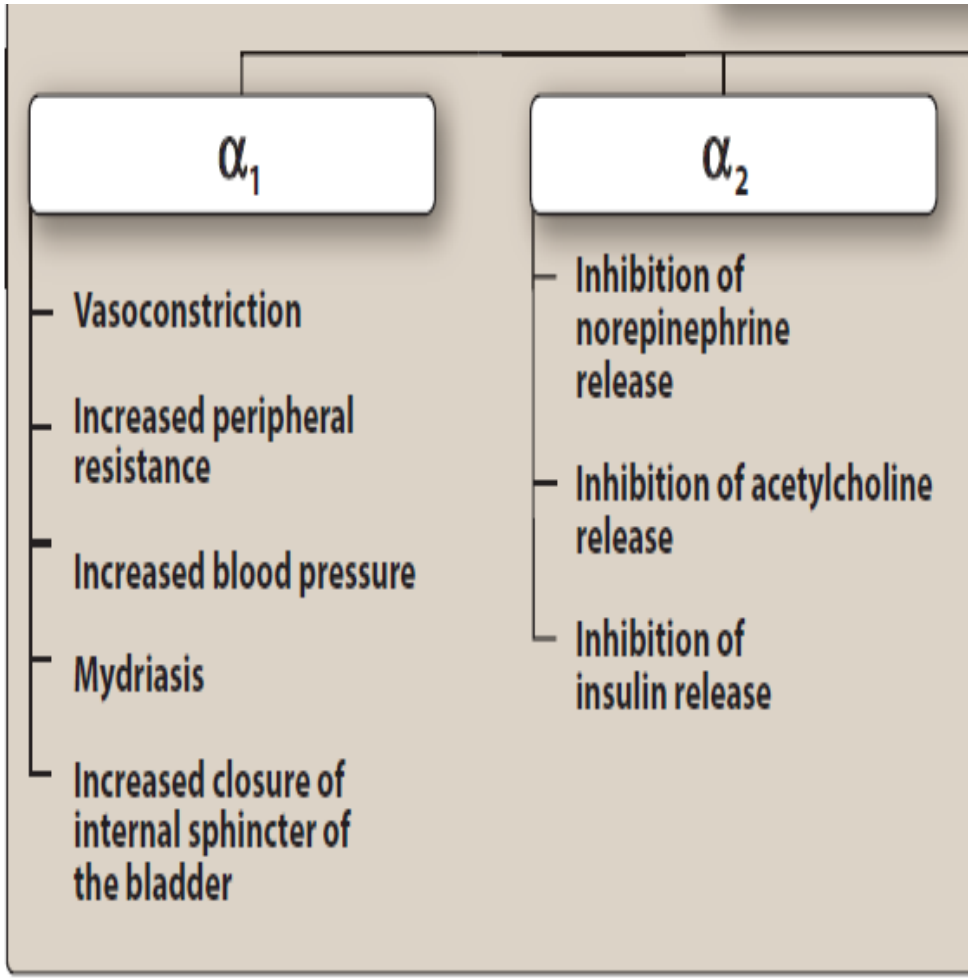
- Therapeutic use: to treat essential hypertension when other desirable medications didn't work

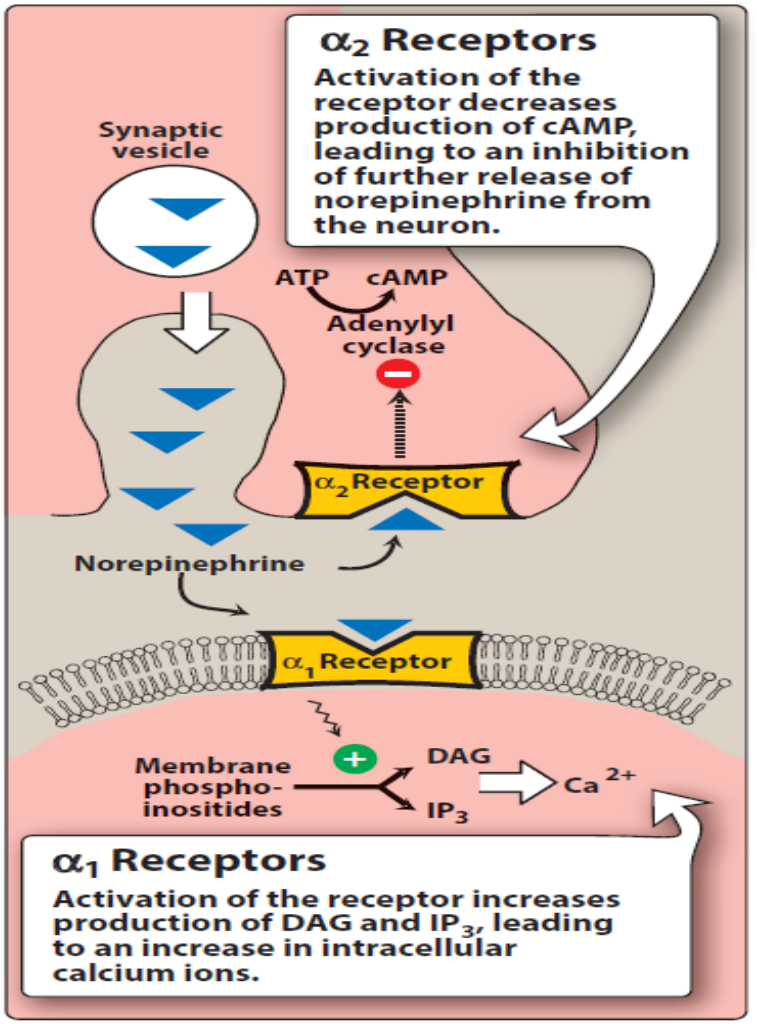
Chapter 17
Adrenergic Agonists

Adrenergic Drugs

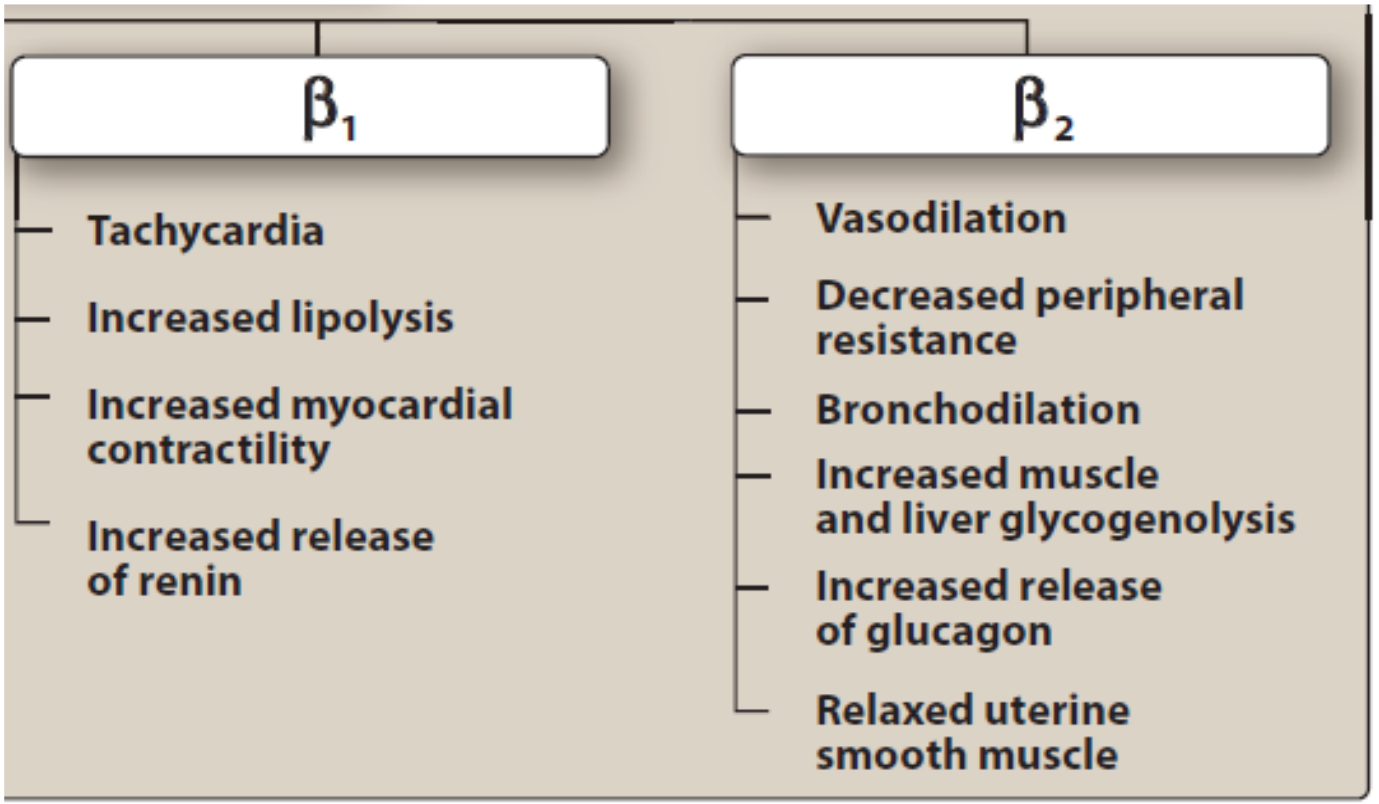
- Adrenergic drugs affect receptors that are stimulated by norepinephrine (noradrenaline) or epinephrine (adrenaline)
- Adrenergic receptors = adrenoceptors
- Drugs activating receptors = sympathomimetics = adrenergic agonists
- Drugs blocking activation of receptors = sympatholytics = adrenergic antagonists

Adrenoceptors





Adrenoceptors



Adrenergic Agonists

- Direct Adrenergic Agonists:
  1. Epinephrine: activating alpha1, alpha2, beta1, and beta2 receptors
  2. Dopamine: activating alpha1, beta1, and dopamine receptors (dose dependent)
  3. Dobutamine: activating beta1 receptor
  4. Phenylephrine: activating alpha1 receptor
  5. Terbutaline, albuterol (salbutamol), salmeterol, formoterol: activating beta2 receptor
- Mixed-Action Adrenergic Agonist
  1. Pseudoephedrine

Adrenergic Agonists

Preadministration Assessment:

- Therapeutic Goal:
  - Epinephrine (IM, IV, subQ, intracardiac, intraspinal, topical, oral inhalation) = treatment of anaphylaxis and cardiac arrest (major use), control superficial bleeding, delay local anesthetic absorption
  - Dopamine (IV) = improve hemodynamic status in patients with shock or heart failure.
  - Dobutamine (IV) = improve hemodynamic status in patients with or heart failure.
  - Phenylephrine = nasal congestion
  - Terbutaline, albuterol (salbutamol), salmeterol, formoterol = asthma
  - Pseudoephedrine = nasal congestion

Adrenergic Agonists

Epinephrine

Preadministration Assessment:

- Identifying high-risk patients: should be used with great caution in patients with hyperthyroidism, cardiac dysrhythmias, organic heart disease, or hypertension. Caution also is needed with patients with angina pectoris or diabetes and in those receiving MAO inhibitors, tricyclic antidepressants, or general anesthetics.

Implementation: Administration:

- Concentration of epinephrine solutions varies – check concentration
- Aspirate prior to IM and subQ administration
- Epinephrine solutions oxidize over time – discard discolored (pink or brown) solutions
- Continuous IV infusion (dopamine + dobutamine)

Adrenergic Agonists

Epinephrine

Ongoing Evaluation and Interventions:

- Evaluating therapeutic effects: in patients receiving IV epinephrine – monitor cardiovascular status continuously
- Minimizing adverse effects:
  - Cardiovascular effects
    - Heart stimulation can cause tachycardia, angina pain, and dysrhythmias – reduced with beta-adrenergic blocking agent (e.g. propranolol)
    - Intense vasoconstriction can occur resulting in severe hypertension – lowered with alpha-adrenergic blocking agent (e.g. phentolamine)
  - Necrosis
    - Extravasation can occur from IV line – necrosis – phentolamine used to minimize injury
  - Hyperglycemia
    - If hyperglycemia develops in diabetic patients – increase insulin dose

Adrenergic Agonists

Epinephrine

Ongoing Evaluation and Interventions:

- Minimizing adverse interactions:
  - Epinephrine dosage require reduction in patients receiving TCA and MAO inhibitors
  - Dysrhythmias may occur in patients receiving anesthetics – relieved with beta1-adrenergic blocker

Chapter 18
Adrenergic Antagonists

Adrenergic Drugs

- Adrenergic drugs affect receptors that are stimulated by norepinephrine (noradrenaline) or epinephrine (adrenaline)
- Adrenergic receptors = adrenoceptors
- Drugs activating receptors = sympathomimetics = adrenergic agonists
- Drugs blocking activation of receptors = sympatholytics = adrenergic antagonists

Adrenergic Antagonists

- **Direct-Acting Antiadrenergic Agents:**
  - **Alpha1-Adrenergic Antagonists:**
    - Tamsulosin, Doxazosin, Alfuzosin, Prazosin, Sildosin, Terazosin
  - **Beta-Adrenergic Antagonists:**
    - First generation – Nonselective beta blockers (block beta1 and beta2):

      Propranolol, Nadolol, Pindolol, Penbutolol, Timolol, Carteolol, Sotalol
    - Second generation – Cardioselective beta blockers (block beta1):

      Metoprolol, Bisoprolol, Atenolol, Esmolol, Acebutolol, Betaxolol
    - Third generation – Beta blockers with vasodilating actions:

      Nebivolol (blocks beta1), Carvedilol (blocks beta1, beta2, alpha1), Labetalol (blocks beta1, beta2, alpha1)
- **Indirect-Acting Antiadrenergic Agents:**
  - **Adrenergic Neuron-Blocking Agent:** Reserpine
  - **Centrally Acting Alpha2 Agonists:** Clonidine and Methyldopa

Adrenergic Antagonists

Alpha1-Adrenergic Antagonists:

Preadministration Assessment:

- Therapeutic Goal:
  - Doxazosin, Prazosin, Terazosin (PO) = reduction of blood pressure in patients with essential (primary) hypertension
  - Tamsulosin, Doxazosin, Terazosin, Alfuzosin, Silodosin (PO) = reduction of symptoms in patients with benign prostatic hyperplasia
- Baseline Data:
  - Essential hypertension = determine blood pressure and heart rate
  - Benign prostatic hyperplasia = determine degree of nocturia, daytime frequency, hesitance, intermittency, terminal dribbing (at the end of voiding), urgency, impairment of size and force of urinary stream, dysuria, and sensation of incomplete voiding
- Identifying High-Risk Patients:
  - Contraindicated in patients with hypersensitivity to these medications

Adrenergic Antagonists

Alpha1-Adrenergic Antagonists:

Implementation: Administration:

- May be taken with food / Tamsulosin administered after eating
- Initial dose at bedtime – to minimize "first-dose" effect

Ongoing Evaluation and Interventions:

- Evaluating Therapeutic Effects:
  - Monitor blood pressure
  - Evaluate for improvement in the symptoms of BPH

Adrenergic Antagonists

Alpha1-Adrenergic Antagonists:

Ongoing Evaluation and Interventions:

- Minimizing Adverse Effects:
  - Orthostatic hypotension (alpha1 blockade)
    - Inform patients about symptoms of hypotension (dizziness, lightheadedness) – advise them to sit or lie down. Advise patients to move slowly when changing from a supine or sitting position to an upright posture
  - First-Dose effect (fainting)
    - Advise patients to avoid driving and other hazardous activities fir 12 to 24 hours – first dose at bedtime

Adrenergic Antagonists

Beta-Adrenergic Antagonists:

Preadministration Assessment:

- Therapeutic Goal:
  - Hypertension, angina pectoris, heart failure, and cardiac dysrhythmias
- Baseline Data:
  - All patients = determine heart rate
  - Hypertension = determine supine and standing BP
  - Angina pectoris = determine incidence, severity, and circumstances of angina attacks
  - Cardiac dysrhythmias = obtain baseline ECG
- Identifying High-Risk Patients:
  - Contraindicated in patients with sinus bradycardia or AV heart block
  - Use with caution (especially nonselective agents) in patients with asthma, bronchospasm, diabetes, or history of allergic reactions
  - Use with caution in patients with history of depression and in those taking calcium channel blockers (verapamil and diltiazem)

Adrenergic Antagonists

Beta-Adrenergic Antagonists:

Implementation: Administration:

- Routes:
  - PO = All beta blockers
  - IV = Atenolol, labetalol, metoprolol, and propranolol
- Administration = warn patients of abrupt discontinuation

Ongoing Evaluation and Interventions:

- Evaluating Therapeutic Effects:
  - Hypertension = advise patients to monitor BP and HR daily
  - Angina pectoris = advise patients to record the incidence, circumstances, and severity of anginal attack
  - Cardiac dysrhythmias = monitor improvement in the ECG

Adrenergic Antagonists

Beta-Adrenergic Antagonists:

Ongoing Evaluation and Interventions:

- Minimizing Adverse Effects:
  - Bradycardia = withhold medication if bradycardia is severe – administer atropine if necessary
  - AV heart block = contraindicated in patients with AV block
  - HF = inform patients about early signs of HF (shortness of breath, night coughs, swelling of the extremities) – instruct them to notify the prescriber
  - Rebound cardiac excitation = warn patients against abrupt discontinuation
  - Postural hypotension = (carvedilol and labetalol) inform patients about hypotension signs (lightheadedness, dizziness) – advise them to sit or lie down. Advise patients to move slowly when changing from a supine or sitting position to an upright posture
  - Bronchoconstriction = risk is lower with *cardioselective agents* in patients with asthma

Adrenergic Antagonists

Beta-Adrenergic Antagonists:

Ongoing Evaluation and Interventions:

- Minimizing Adverse Effects:
  - Effects in Diabetic Patients =
    - Cardioselective agents are preferred
    - Insulin-induced hypoglycemia can trigger glycogenolysis – prevented by beta2 blockade
    - Insulin-induced hypoglycemia – insulin dose may be reduced in patients with beta blockers
    - Tachycardia is an early sign of hypoglycemia – can be masked by beta1 blockade
    - Warn patients that tachycardia cannot be relied on as an indicator for hypoglycemia if they are receiving beta blockers – teach them to recognize other symptoms (sweating, fatigue, hunger, poor concentration)

Adrenergic Antagonists

Beta-Adrenergic Antagonists:

Ongoing Evaluation and Interventions:

- Minimizing Adverse Interactions:
    - CCB's must be used with caution
    - Diabetic patients may require to decrease insulin dose

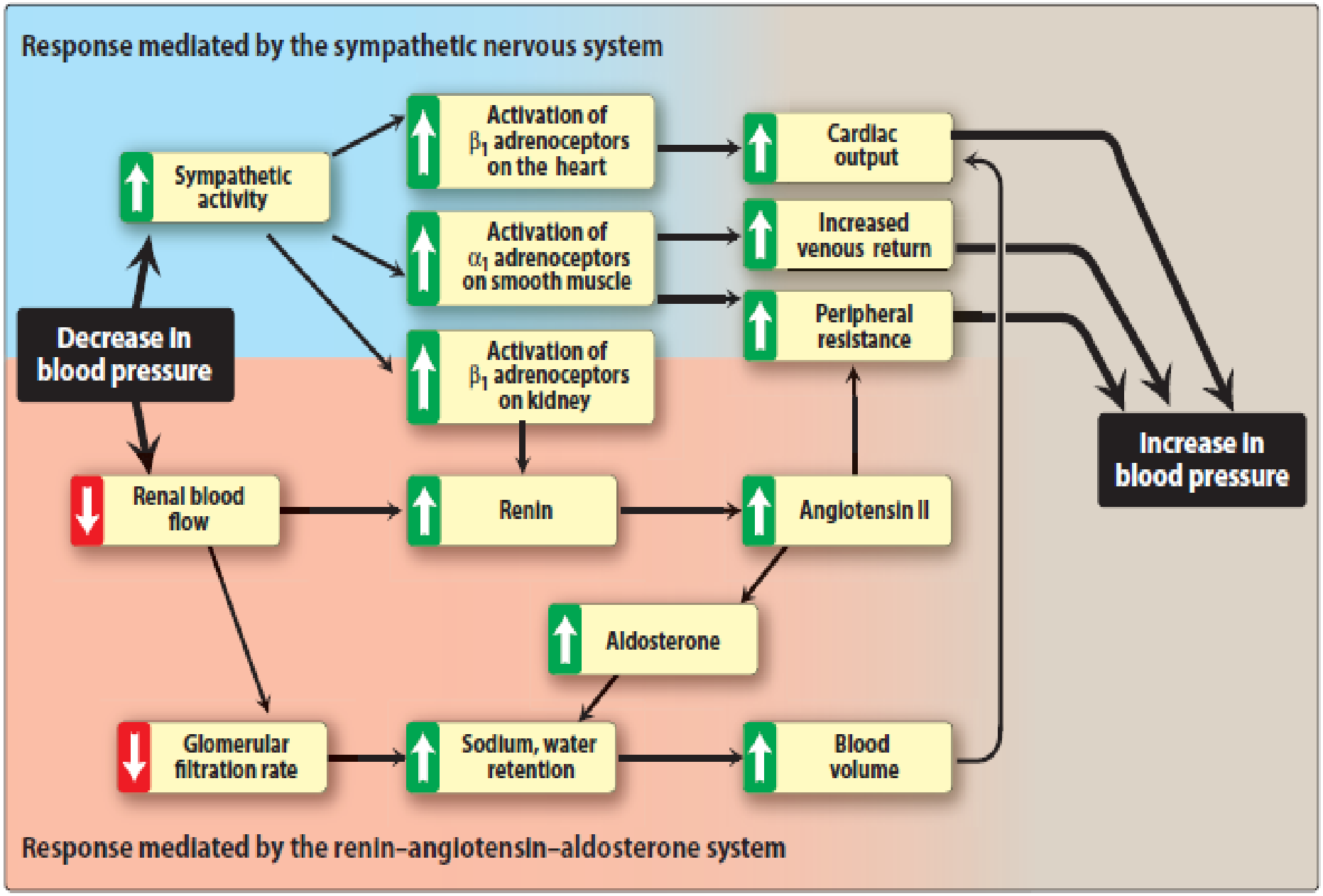
Chapter 47
Drugs for Hypertension

Hypertension

- **Essential (Primary) Hypertension** (elevated blood pressure [BP]): hypertension without identifiable cause – most common form of hypertension.

- Hypertension:
  - ≥140/90 mmHg for patients without clinical CVD and low risk
  - ≥130/80 mmHg for patients with comorbidities (DM, chronic kidney disease)

- To reduce BP: **Therapeutic goal for all patients is <130/80 mmHg**
  - Lifestyle modifications (weight reduction, smoking cessation, reduction of salt and alcohol intake, follow DASH diet, aerobic exercise)
  - Drug therapy


Response mediated by the sympathetic nervous system
Sympathetic activity
Activation of β_1 adrenoceptors on the heart
Activation of α_1 adrenoceptors on smooth muscle
Activation of β_1 adrenoceptors on kidney
Cardiac output
Increased venous return
Peripheral resistance
Decrease in blood pressure
Increase in blood pressure
Renal blood flow
Renin
Angiotensin II
Aldosterone
Glomerular filtration rate
Sodium, water retention
Blood volume
Response mediated by the renin–angiotensin–aldosterone system

Classes of Antihypertensive Drugs

- **Main Drug Classes:**
  - Diuretics
  - Beta blockers
  - Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)
  - Angiotensin II Receptor Blockers (ARBs)
  - Calcium Channel Blockers (CCBs)
  - Aldosterone Antagonists

Classes of Antihypertensive Drugs

- **Diuretics:**
  - Thiazide diuretics: e.g. hydrochlorothiazide
  - Loop diuretics: e.g. furosemide
  - Potassium-sparing diuretics: e.g. spironolactone
- **Beta Blockers**: (as discussed before)
- **ACE Inhibitors**: e.g. captopril, enalapril
- **ARBs**: e.g. candesartan, valsartan
- **CCBs**: e.g verapamil, diltiazem
- **Aldosterone Antagonists**: e.g. eplerenone, spironolactone

Antihypertensive Drugs

Preadministration Assessment:

- Therapeutic Goal:
  - Prevent long-term consequences of hypertension (heart disease, kidney disease, stroke)
  - <130/80 mmHg for all patients

- Baseline Data:
  - All patients: BP, ECG, complete urinalysis, hemoglobin and hematocrit, and blood levels of sodium, potassium, calcium, creatinine, glucose, uric acid, TG, and cholesterol

- Identifying High-Risk Patients: (e.g.)
  - Patients with AV block, bradycardia, or asthma – beta blockers contraindicated
  - Patients with gout or diabetes – thiazide diuretics must be used with caution

Antihypertensive Drugs

Implementation: Administration:

- Routes: Chronic hypertension – all are PO (none is injected)
- Dosage:
  - Dosages should be low initially and then gradually increased

Implementation: Measures to Enhance Therapeutic Effects:

- Lifestyle modifications: should be tried for 6-12 months before implementing drug therapy and continued even if drug therapy is required
  - Weight reduction: Help overweight patients to develop an exercise program and a restricted-calorie diet – BMI goal is in the normal range (18.5-24.9)
  - Sodium restriction: Encourage patients to consume no more than 6g of salt
  - DASH diet
  - Alcohol restriction: limits to 1 ounce/day for men and 0.5 ounce/day for women and lighter weight men
  - Exercise: Encourage patients to perform aerobic exercises (walking, jogging, swimming, bicycling) for 30-45 minutes most days of the week
  - Smoke cessation

Antihypertensive Drugs

Ongoing Evaluation and Interventions:

- Evaluating treatment:
  - Monitor BP periodically – goal is <130/80 mmHg
  - Teach patients to self-monitor their BP and maintain a BP record

- Minimizing adverse effects/interactions:
  - Dosages should be low initially and then gradually increased
  - Patients with AV block, bradycardia, or asthma – beta blockers contraindicated
  - Patients with gout or diabetes – thiazide diuretics must be used with caution
  - Patients with hyperkalemia – Potassium-sparing diuretics, ACE inhibitors, ARBs, aldosterone antagonists can cause further potassium accumulation

Antihypertensive Drugs

Ongoing Evaluation and Interventions:

- Minimizing adverse effects/interactions:
  - Patients with hypokalemia – Thiazides and loop diuretics can cause further potassium loss

- Notes:
  - ACE inhibitors, ARBs, or aldosterone antagonists should not be added with potassium-sparing diuretics (hyperkalemia)
  - ACE inhibitors and ARBs should not be combined
  - ACE inhibitors, ARBs, and aldosterone antagonists are contraindicated in pregnancy

Chapter 51
Drugs for Angina Pectoris

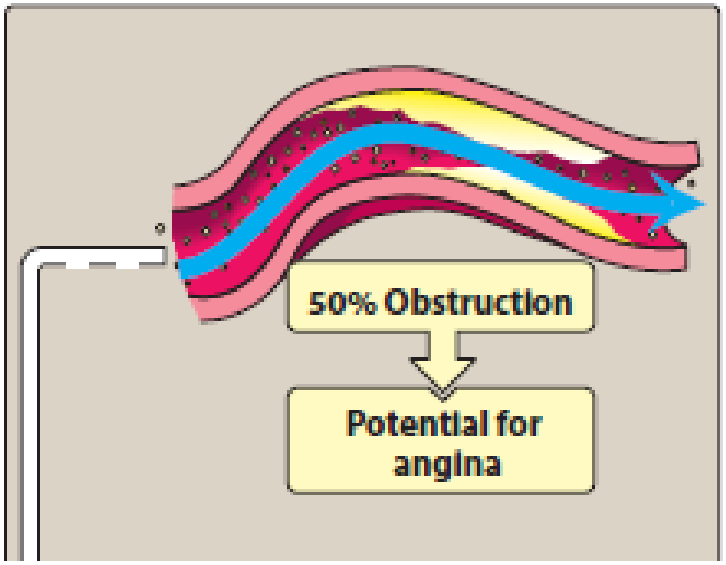
Angina Pectoris

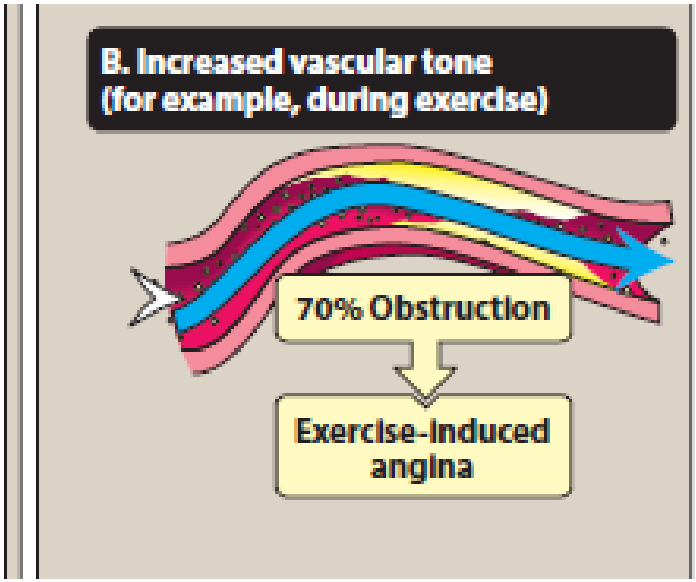
- **Angina pectoris**: sudden pain beneath the sternum, often radiating to the left shoulder and arm.
- Anginal pain occurs when the cardiac oxygen supply is insufficient to meet oxygen demand.

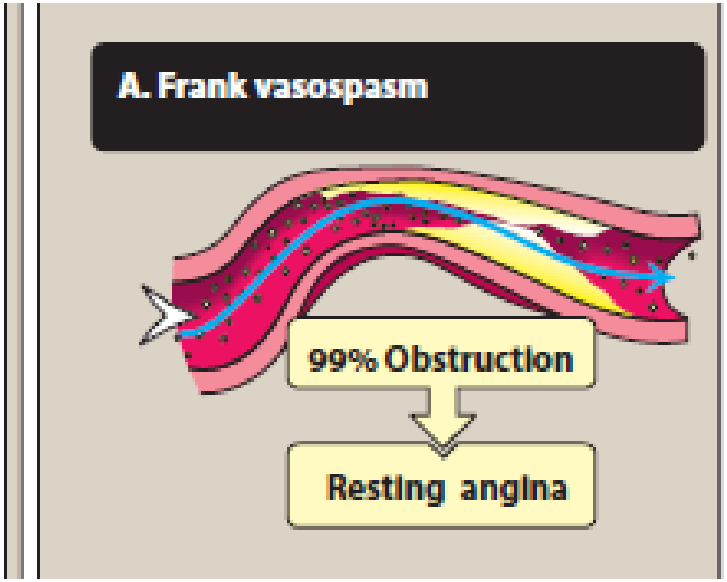
- *Cardiac oxygen demand* is determined by = HR / contractility / preload / afterload. *Reduced by drugs – relieve anginal pain*

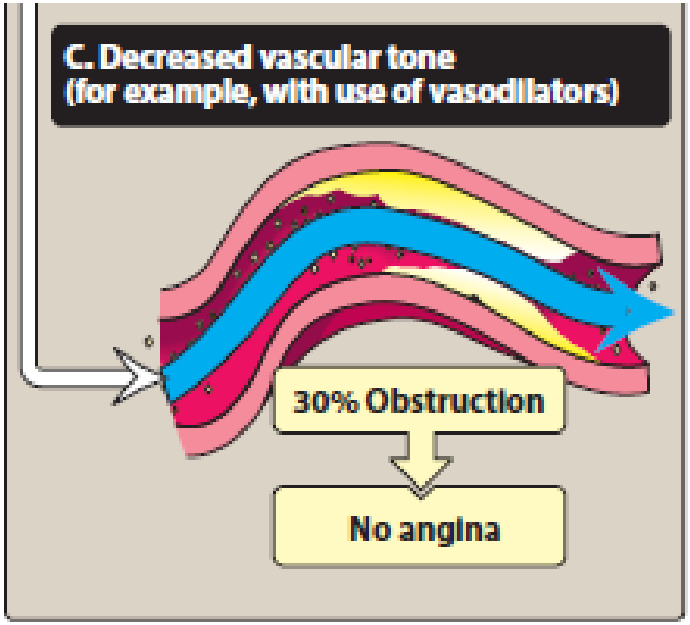
- *Cardiac oxygen supply* is determined by = myocardial blood flow. *Increased by drugs – reduce anginal pain*

- 3 forms of Angina Pectoris
  - Chronic Stable Angina (angina of effort / exercise-induced angina)
  - Variant (vasospastic) Angina
  - Unstable angina


50% Obstruction
Potential for angina


B. Increased vascular tone
(for example, during exercise)
70% Obstruction
Exercise-induced angina


A. Frank vasospasm
99% Obstruction
Resting angina


C. Decreased vascular tone
(for example, with use of vasodilators)
30% Obstruction
No angina

Angina Pectoris

- Coronary artery atherosclerosis – stable angina
- Coronary artery spasm – variant angina

- Drugs decreasing oxygen demand – relieve pain of stable angina
- Drugs increasing oxygen supply – relieve pain of variant angina

- Treatment objectives for patients with chronic stable angina:
  1. Prevention of MI and death – treatment with cholesterol-lowering drugs and antiplatelet drugs (e.g. aspirin).
  2. Prevention of anginal pain (as above)

- Revascularization with CABG surgery or PCI – if two or three antianginal drugs has failed

Angina Pectoris

- Anginal Pain is prevented with:
  - One or more long-acting antianginal drugs
    - **Beta blockers** (propranolol, metoprolol) (chronic stable angina)
    - **CCBs** (verapamil, diltiazem, nifedipine, amlodipine) (chronic stable angina + variant angina)
    - **Long-acting nitrate** (vasodilators) (e.g. isosorbide mononitrate and isosorbide dinitrate) (chronic stable angina + variant angina)
  - + **sublingual nitroglycerin** (vasodilator) (chronic stable angina + variant angina) when breakthrough pain occurs

- **Ranolazine** should not be used alone; used with beta blocker, nitrate, or the CCB amlodipine

- Ranolazine reduces accumulation of sodium and calcium in myocardial cells – might help myocardium use energy more sufficiently

Angina Pectoris

Nitroglycerin

Preadministration Assessment:

- Therapeutic Goal: Reduction of the frequency and intensity of angina attacks

- Baseline Data:
  - Obtain baseline data on frequency and intensity of anginal attacks, location of anginal pain, and risk factors (HTN, hyperlipidemia)

- Identifying High-Risk Patients:
  - Use with caution in hypotensive patients and patients taking antihypertensive medications and alcohol (may produce excessive lowering of BP)
  - Use with sildenafil or other PDE5 inhibitors is *contraindicated*

Angina Pectoris

Nitroglycerin

Implementation: Administration:

- Routes and Administration:
  - Sublingual tablets
    - Use = prophylaxis or termination of acute angina attack
    - Technique of administration =
      - Instruct patients to leave tablet under tongue – until dissolved
      - Tablet should not be swallowed
      - Instruct patients to call emergency if pain not relieved after 5mins – (while waiting) take another tablet – and a 3rd tablet after 5mins if still not relieved
      - Instruct patients to store tablets in dark, tightly closed bottle that contains no other medication
      - Unused medication to be discarded after 24 months
  - Other routes
    - Sustained-release oral capsules / transdermal delivery systems / translingual spray / transmucosal (buccal) tablets / topical ointment / IV

Angina Pectoris

Nitroglycerin

Implementation: Measures to Enhance Therapeutic Effects:

- Reducing risk factors:
  - Precipitating factors: advise patients to avoid overexertion, heavy meals, emotional stress, cold exposure
  - Weight reduction
  - Exercise (aerobic exercise)
  - Smoking cessation
  - Treatment for HTN or hypercholesterolemia

Ongoing Evaluation and Interventions:

- Evaluating therapeutic effects:
  - Have the patient keep a record of the frequency and intensity of anginal attacks, location of anginal pain, and risk factors

Angina Pectoris

Nitroglycerin

Ongoing Evaluation and Interventions:

- Minimizing adverse effects:
  - Headache:
    - Inform patients that headache will diminish with continued drug use – relieved with aspirin, paracetamol
  - Orthostatic hypotension
    - Inform patients about symptoms of hypotension (dizziness, lightheadedness) – advise them to sit or lie down. Advise patients to move slowly when changing from a supine or sitting position to an upright posture (minimize hypotension)
  - Reflex tachycardia
    - Can be suppressed with concurrent treatment with beta blocker, verapamil, or diltiazem

Angina Pectoris

Nitroglycerin

Ongoing Evaluation and Interventions:

- Minimizing adverse interactions:
  - Advise patients to avoid alcohol
  - Caution required when using nitroglycerin with medications that lower BP (beta blockers, diuretics, CCBs, etc..)
  - Nitroglycerin contraindicated with all PDE5 inhibitors

- Notes:
  - Isosorbide mononitrate and isosorbide dinitrate have similar implications as nitroglycerin (differ only by dosage forms, routes of administration, and time course of action)

Chapter 52
Anticoagulant, Antiplatelet, and Thrombolytic Drugs

Introduction

- **Hemostasis**: physiologic process by which bleeding is stopped

- Hemostasis involves:

1. Formation of a platelet plug, followed by
2. Coagulation (fibrin production)

- **Hemorrhage**: bleeding

- This chapter deals with drugs that are used to prevent formation of thrombi (intravascular blood clots) and dissolve thrombi that have already formed. It also covers drugs to prevent bleeding.

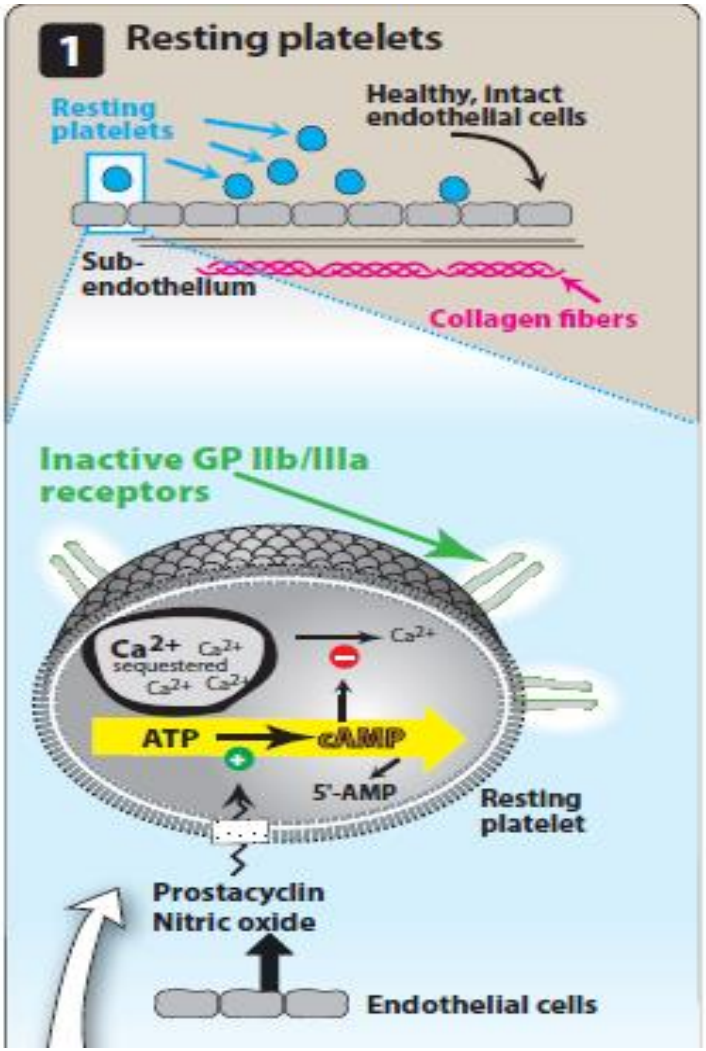
Introduction

- Thrombosis: thrombus formation / reflects the pathologic functioning of hemostatic mechanisms
- Thrombus: a blood clot formed within a blood vessel or heart / adheres to a blood vessel wall
- Detached thrombus / Embolus: Intravascular clot that floats in the blood
- Thrombus/embolus = block blood vessels – affect oxygen and nutrients supply.

Introduction

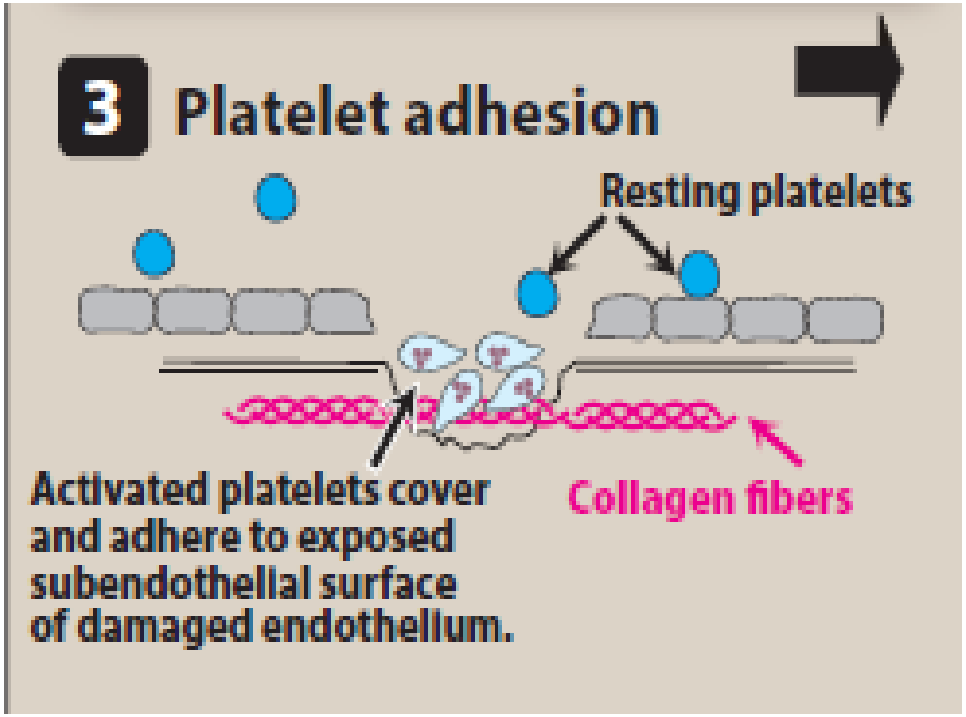
- Examples of thrombotic disorders = acute myocardial infarction (MI), deep vein thrombosis (DVT), pulmonary embolism (PE), and acute ischemic stroke
- Arterial thrombosis = platelet-rich clot
- Venous thrombosis = fibrin-rich clot with fewer platelets
- Examples of bleeding disorders = hemophilia, fibrinolytic states that may rise after surgeries, high doses of anticoagulants, and vitamin K deficiency

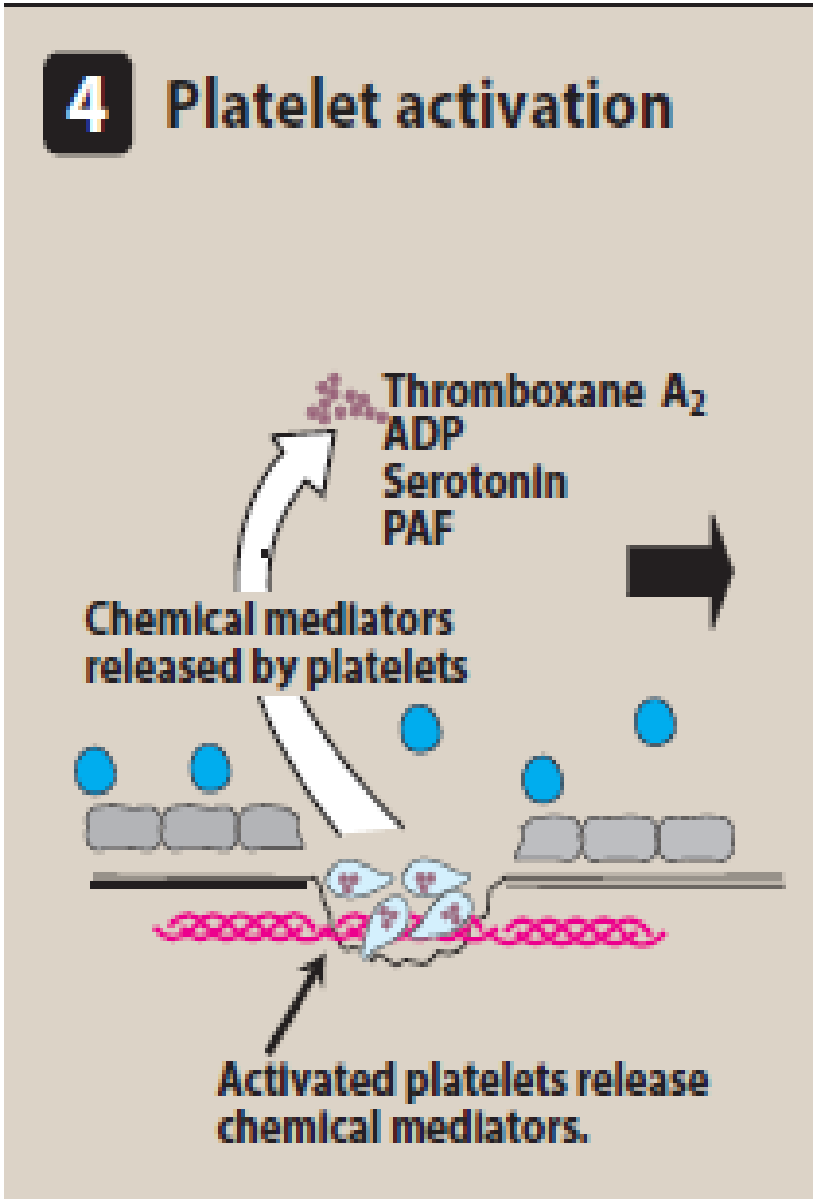
Platelet Response to Vascular Injury

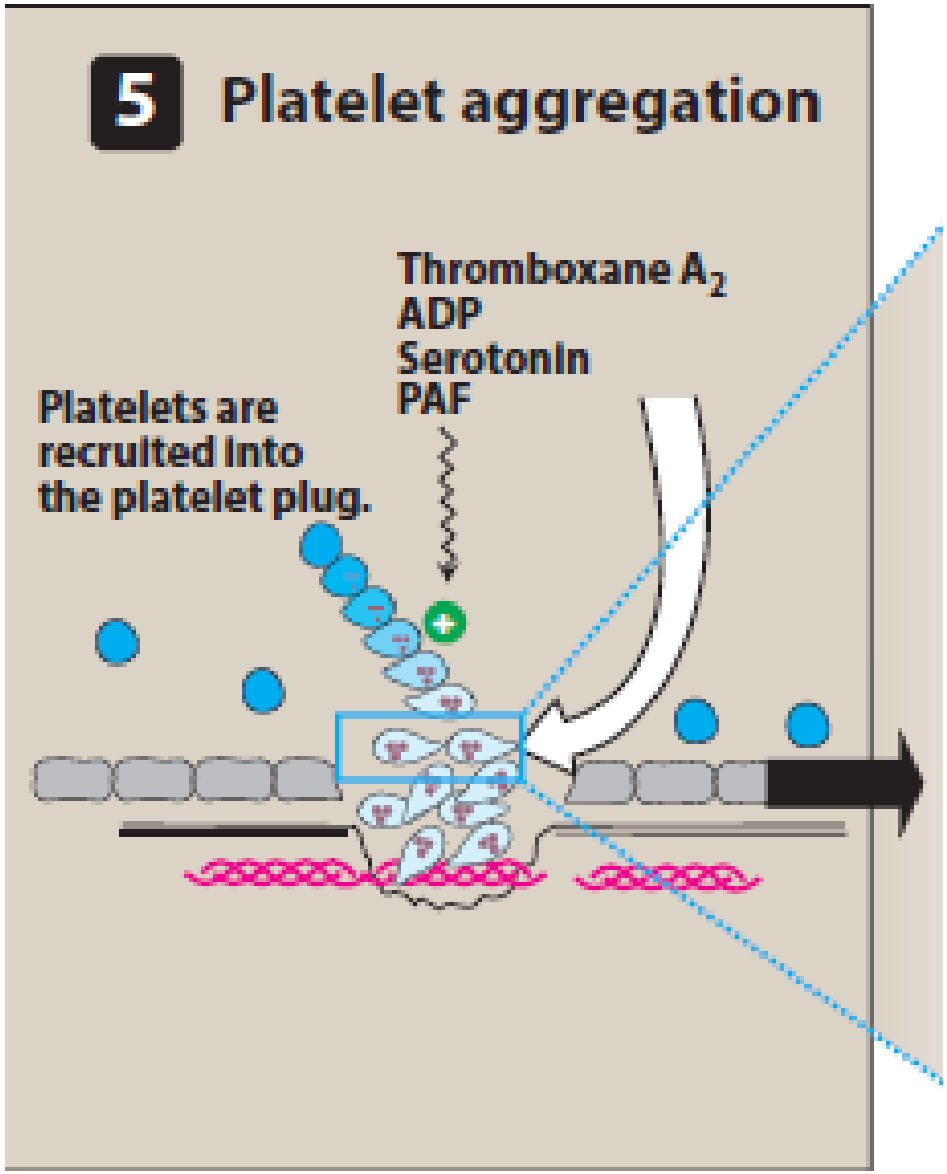


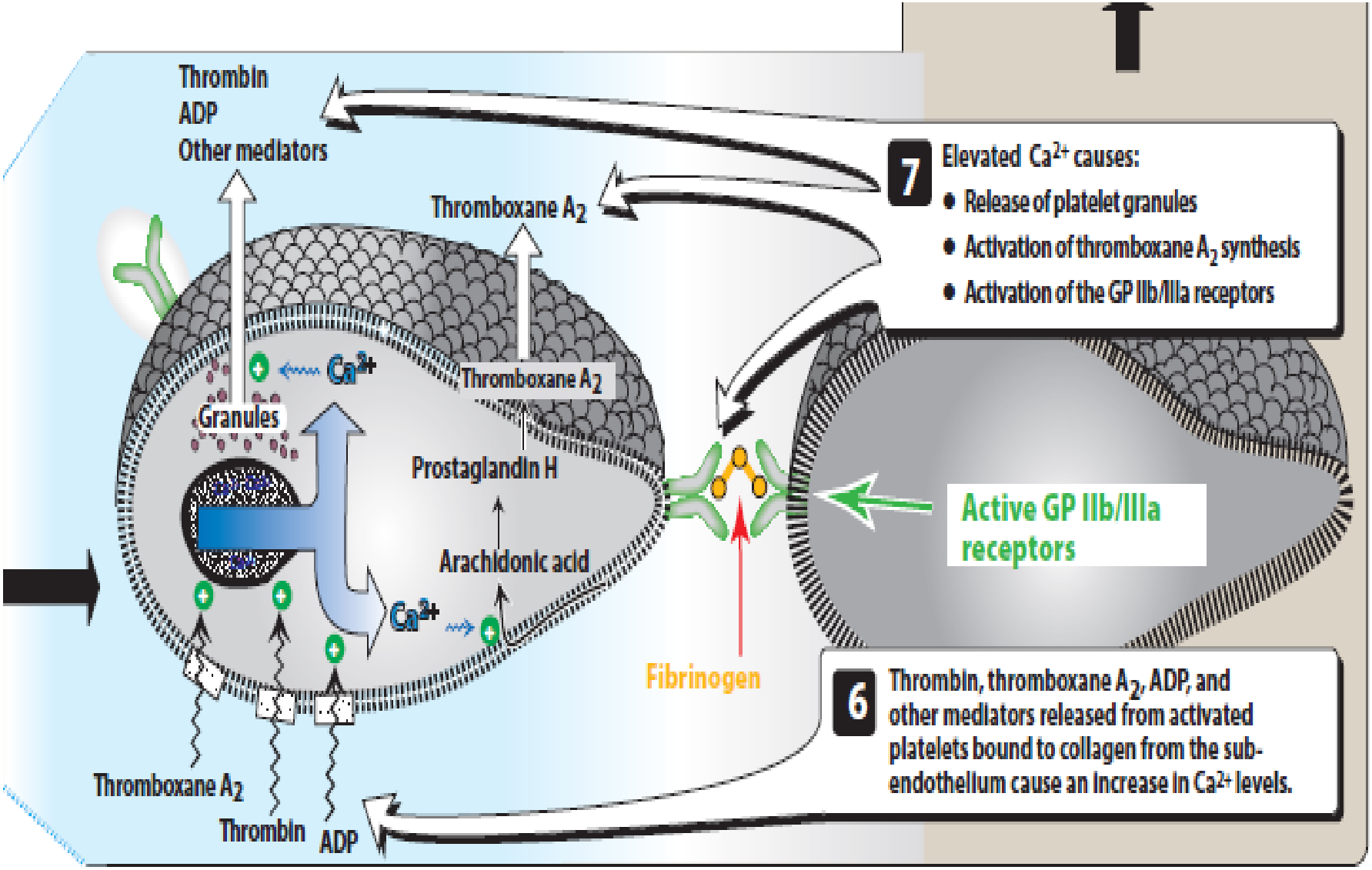
2

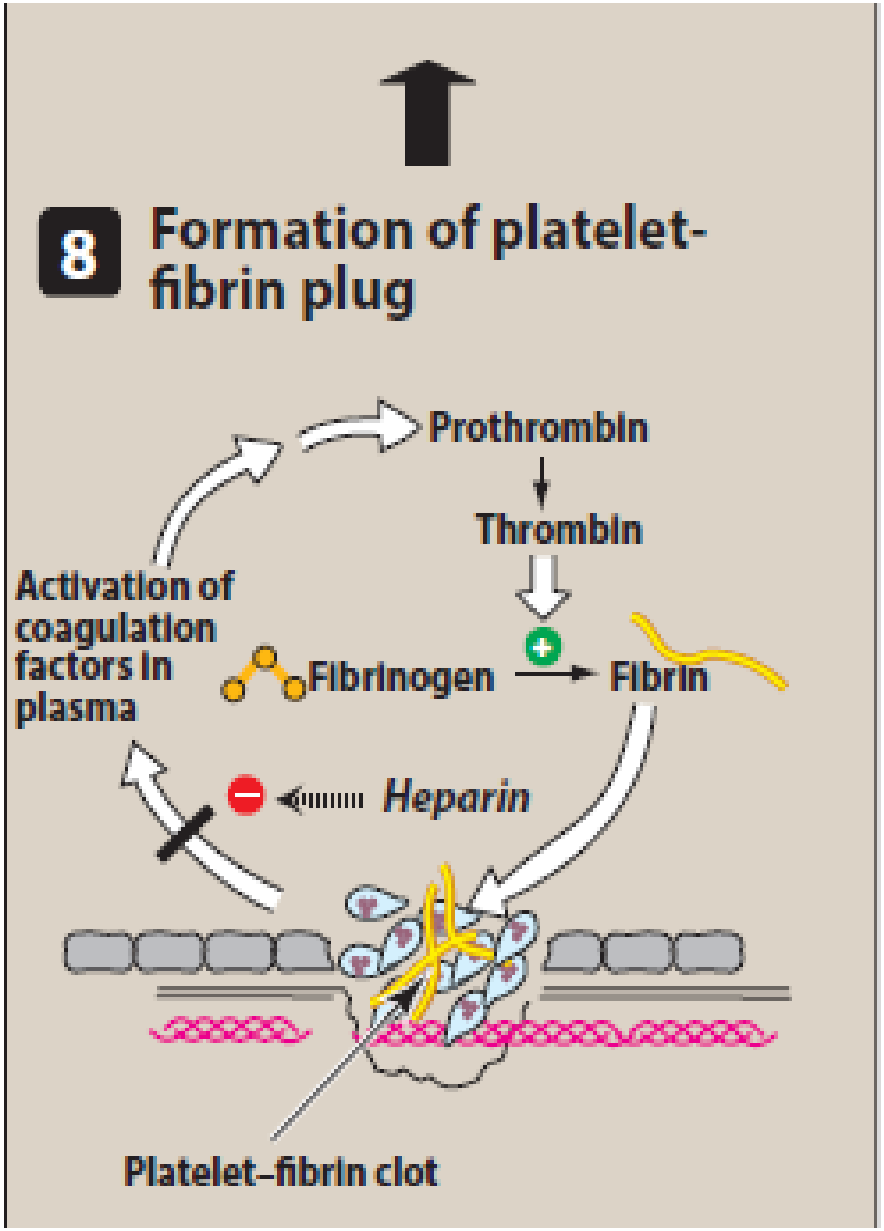
- Healthy, intact endothelium releases prostacyclin into plasma.
- Prostacyclin binds to platelet membrane receptors, causing synthesis of cAMP.
- cAMP stabilizes inactive GP IIb/IIIa receptors and inhibits release of granules containing platelet aggregation agents or Ca^{2+}.

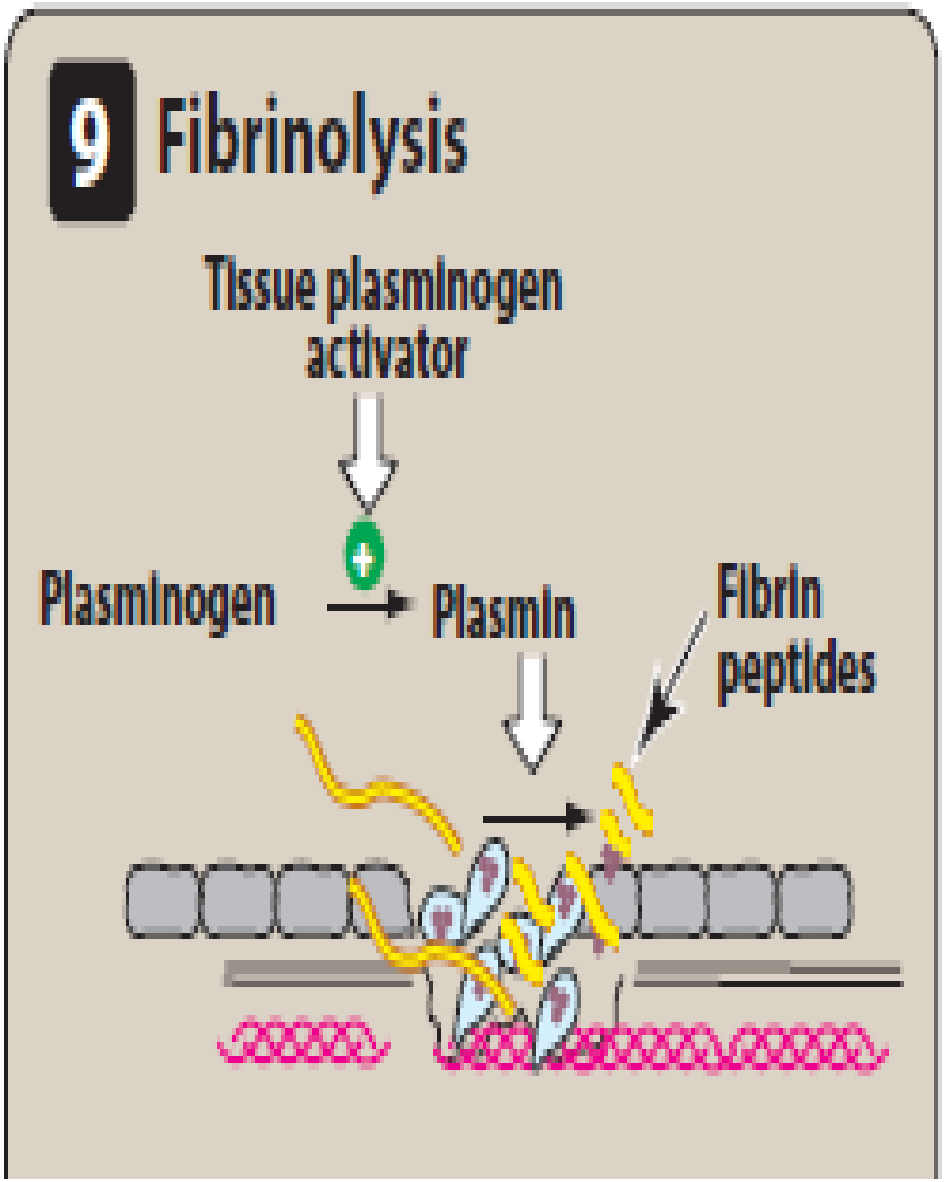

3 Platelet adhesion
Resting platelets
Activated platelets cover and adhere to exposed subendothelial surface of damaged endothelium.
Collagen fibers


4 Platelet activation
Thromboxane A_2
ADP
Serotonin
PAF
Chemical mediators released by platelets
Activated platelets release chemical mediators.


5 Platelet aggregation
Thromboxane A_2
ADP
Serotonin
PAF
Platelets are recruited into the platelet plug.


Thrombin
ADP
Other mediators
Thromboxane A2
Ca2+
Granules
Thromboxane A2
Prostaglandin H
Arachidonic acid
Ca2+
Thromboxane A2
Thrombin
ADP
7
Elevated Ca2+ causes:
Release of platelet granules
Activation of thromboxane A2 synthesis
Activation of the GP IIb/IIIa receptors
Active GP IIb/IIIa receptors
Fibrinogen
6
Thrombin, thromboxane A2, ADP, and other mediators released from activated platelets bound to collagen from the sub-endothelium cause an increase in Ca2+ levels.


8 Formation of platelet-fibrin plug
Prothrombin
Thrombin
Activation of coagulation factors in plasma
Fibrinogen
Fibrin
Heparin
Platelet–fibrin clot


9 Fibrinolysis
Tissue plasminogen activator
Plasminogen
Plasmin
Fibrin peptides

Anticoagulants

- **Heparin (Unfractionated) and low molecular weight heparins (LMWH – e.g. Enoxaparin, dalteparin, tinzaparin)**
- **Selective Factor Xa Inhibitors (e.g. Fondaparinux, Rivaroxaban)**
- **Direct Thrombin Inhibitors (e.g. Dabigatran, Bivalirudin, Lepirudin, Argatroban, Desirudin)**
- **Warfarin**

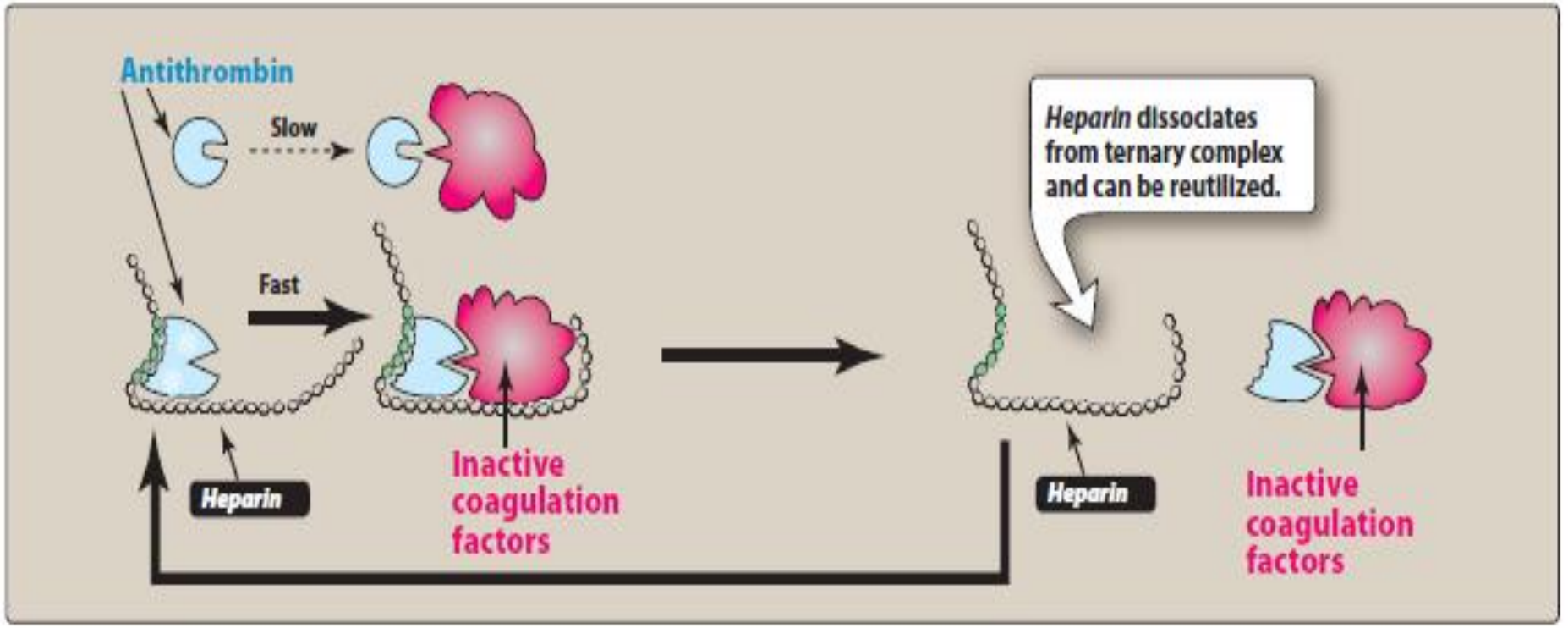
Anticoagulants

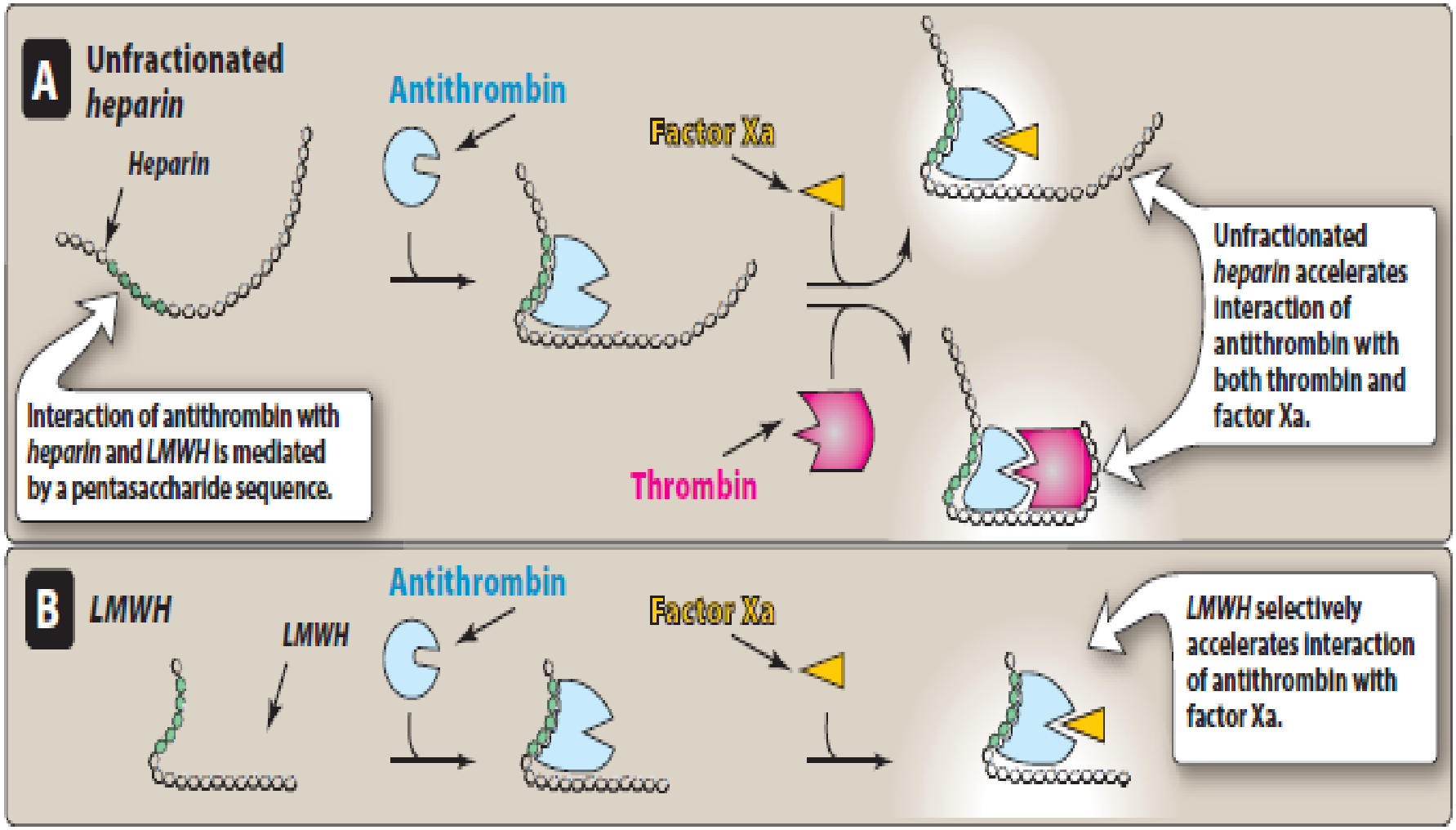
Heparin (Unfractionated) and low molecular weight heparins (LMWH – e.g. Enoxaparin, dalteparin, tinzaparin):

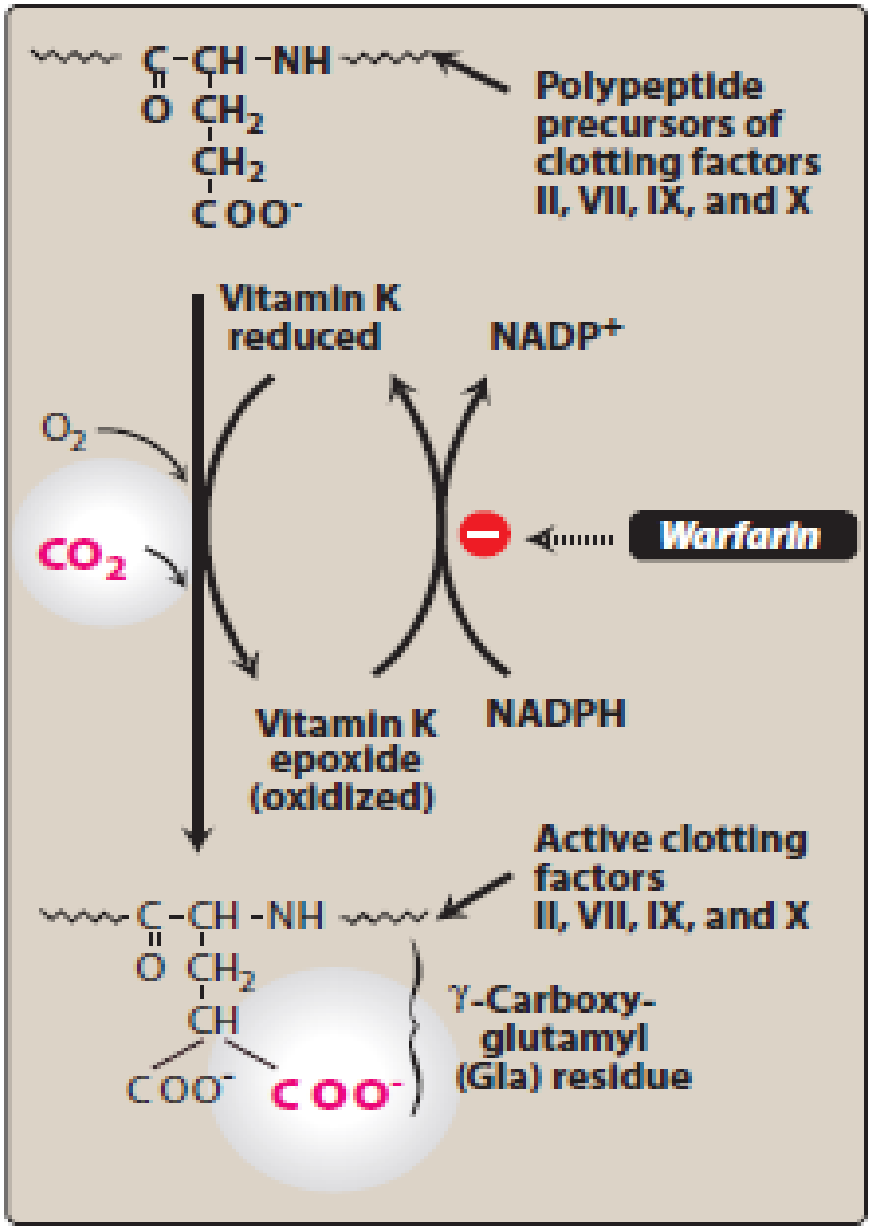
- Activates antithrombin, which then inactivates thrombin (only heparin) and factor Xa (heparin and LMWH)

Warfarin:

- Suppresses coagulation by decreasing production of four clotting factors: prothrombin (II), VII, IX, and X. These are called vitamin K-dependent clotting factors.


Antithrombin
Slow
Fast
Heparin
Inactive coagulation factors
Heparin dissociates from ternary complex and can be reutilized.
Heparin
Inactive coagulation factors


A
Unfractionated heparin
Heparin
Antithrombin
Factor Xa
Thrombin
Interaction of antithrombin with heparin and LMWH is mediated by a pentasaccharide sequence.
Unfractionated heparin accelerates interaction of antithrombin with both thrombin and factor Xa.
B
LMWH
LMWH
Antithrombin
Factor Xa
LMWH selectively accelerates interaction of antithrombin with factor Xa.


Polypeptide precursors of clotting factors II, VII, IX, and X
Vitamin K reduced
NADP+
O2
CO2
Warfarin
Vitamin K epoxide (oxidized)
NADPH
Active clotting factors II, VII, IX, and X
γ-Carboxy-glutamyl (Gla) residue

Anticoagulants

Heparin

Preadministration Assessment:

- Therapeutic Goal:
  - Prevent venous thrombosis without inducing spontaneous bleeding
  - Used during pregnancy, pulmonary embolism, massive DVT, evolving stroke, open heart surgery, renal dialysis

- Baseline Data:
  - Obtain baseline values for BP, HR, complete blood counts, platelet counts, hematocrit and aPTT

- Identifying High-Risk Patients:
  - *Contraindicated* for patients with severe thrombocytopenia or uncontrollable bleeding, for patients undergoing lumbar puncture, regional anesthesia, or surgery of the eye, brain, or spinal cord.
  - *Caution* is needed in patients with high risk of bleeding, GI ulcers, severe hypertension, severe hepatic or renal dysfunction

Anticoagulants

Heparin

Implementation: Administration:

- Routes: IV (continuous infusion or intermittent) and subQ. Avoid IM injections.
- Administration:
  - General Consideration: Dose in *units* **NOT** *milligrams* – read label carefully
  - Intermittent IV administration:
    - administer through heparin lock every 4 to 6 hours
    - Determine aPTT before each dose during early phase of treatment, and then daily
    - Rotate injection site every 2 to 3 days
  - Continuous IV infusion:
    - Administer with an infusion pump – check infusion rate every 30 to 60 minutes
    - aPTT should be determined every 4 hours during the early phase of treatment
    - Check site of needle insertion periodically for extravasation

Anticoagulants

Heparin

Implementation: Administration:

- Administration:
  - Deep subQ injection:
    - Fatty layer of the abdomen (not within 2 inches of the umbilicus)
    - Draw up heparin solution using large needle, then discard the needle and replace it with a small needle
    - Apply gentle pressure to the injection site for 1 to 2 minutes
    - Rotate and record injection sites

Ongoing Evaluation and Interventions:

- Evaluating Treatment:
  - aPTT – heparin increase the aPTT by *1.5-2 fold above baseline*
- Minimizing adverse effects:
  - Hemorrhage: check signs of bleeding – if occurred, heparin should stopped – severe bleeding treated with slow IV infusion with *protamine sulfate* / risk reduced if *aPTT not exceeding 2 times the baseline value*

Anticoagulants

Heparin

Ongoing Evaluation and Interventions:

- Minimizing adverse effects:
  - Heparin-induced thrombocytopenia: reduced platelet counts leading to increased risk of thrombotic event – monitor platelet count – discontinue if severe thrombocytopenia developed
  - Hypersensitivity reactions: allergy may develop from heparin preparations – *small test dose before the therapeutic dose*

- Minimizing adverse interactions:
  - Antiplatelet drugs: use these agent with caution if heparin is used

Anticoagulants

Warfarin

Preadministration Assessment:

- Therapeutic Goal:
  - Prevent venous thrombosis without inducing spontaneous bleeding
  - Prevention of venous thrombosis, pulmonary embolism, thromboembolism in patients with prosthetic heart valves, and thrombosis during atrial fibrillation.
- Baseline Data:
  - Obtain baseline values for BP, HR, complete blood counts, platelet counts, hematocrit and PT. Genetic testing for variants of CYP2C9 or VKORC1.

- Identifying High-Risk Patients:
  - *Contraindicated* for patients with vitamin K deficiency, liver disease, alcoholism, thrombocytopenia, uncontrollable bleeding, pregnancy, lactation, patients undergoing lumbar puncture, regional anesthesia, or surgery of the eye, brain, or spinal cord.
  - Use in *caution* with patients at high risk of bleeding and patients with variant forms of CYP2C9 or VKORC1.

Anticoagulants

Warfarin

Implementation: Administration:

- Route: Oral
- Administration:
  - Dosage is adjusted to maintain an INR value of 2 to 3

Implementation: Measures to Enhance Therapeutic Effects:

- Promoting adherence:
  - Provide patient with detailed written and verbal instructions regarding purpose of treatment, dosage size and timing, and importance of strict adherence
  - Providing a chart to record warfarin use
  - Incompetent patients – supervised by a responsible individual
- Nondrug measures:
  - Avoid prolonged immobility
  - Raise legs when sitting
  - Avoid garments that restrict blood flow to legs
  - Exercise

Anticoagulants

Warfarin

<u>Ongoing Evaluation and Interventions:</u>

- Evaluating therapeutic effects:
  - Monitoring prothrombin time:
    - monitor PT – reported as INR (target 2-3)
    - Adjust doses if INR not within target
    - Monitor frequently
    - If heparin is concurrently used – caution when taking blood for PT determinations

Anticoagulants

Warfarin

Ongoing Evaluation and Interventions:

- Minimizing adverse effects:
  - Hemorrhage:
    - Inform patients about bleeding signs – instruct patients to withhold warfarin and notify prescriber
    - Advise patients to wear Medic Alert bracelet – indicating warfarin use
    - Advise patients to avoid excessive alcohol consumption
    - Advise patients to use soft toothbrush
    - Advise patients to shave with electric razor
    - For surgeries – make sure the surgeon is aware of warfarin use
    - Warfarin should be discontinued several days before surgeries
    - Vitamin K could be used if emergency surgery is required
  - Use in pregnancy and lactation:
    - Warfarin can cross placenta (risks to fetus) and enters breast milk – warn women of child-bearing age against becoming pregnant and breast-feeding

Antiplatelet Drugs

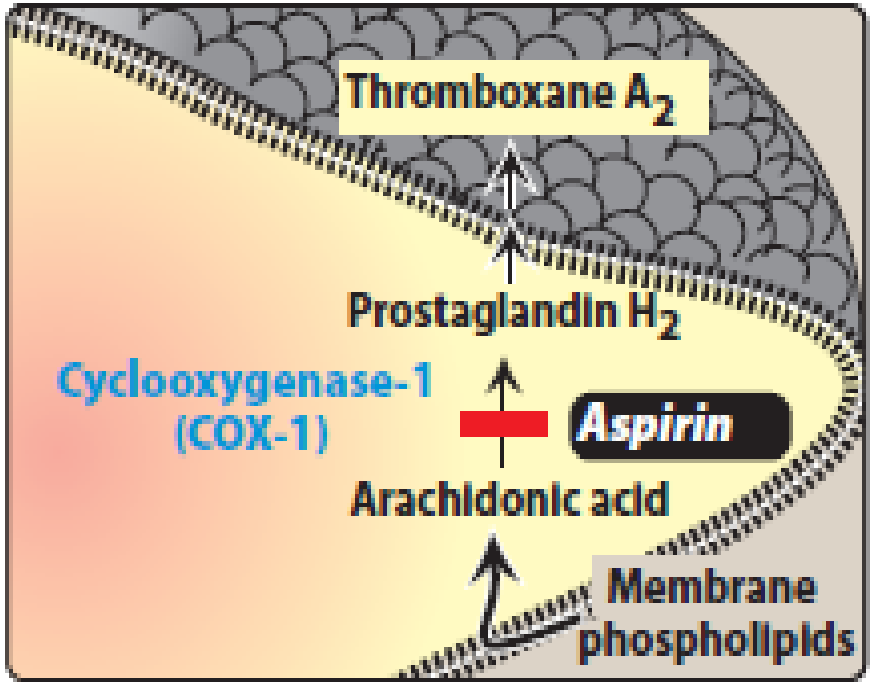
- Antiplatelet drugs:

1. Aspirin
2. Adenosine diphosphate (ADP) receptor antagonists (e.g. clopidogrel, ticlopidine, prasugrel)
3. Glycoprotein (GP) IIb/IIIa receptor antagonists (e.g. abciximab, eptifibatide, tirofiban)

- Suppress thrombus formation in arteries

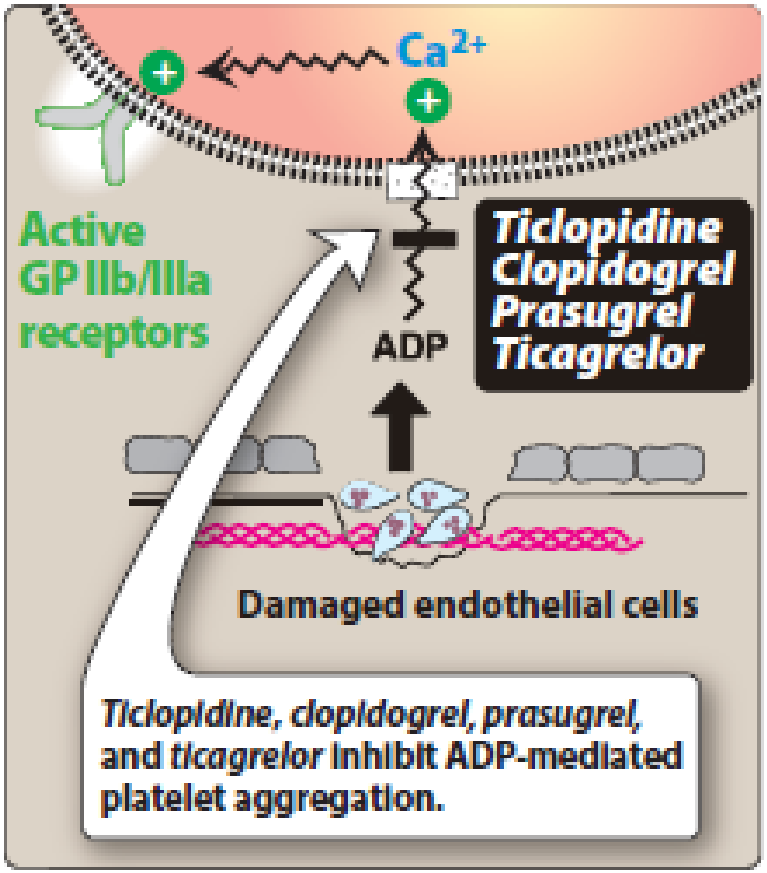
Antiplatelet Drugs

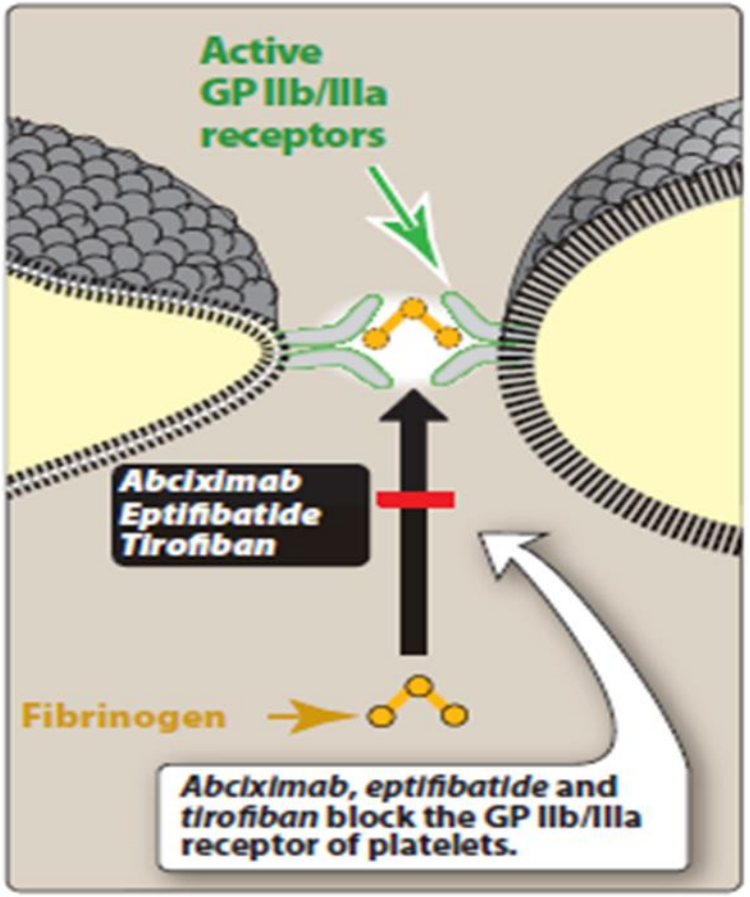
- **Aspirin**:
- Irreversible inhibition of cyclooxygenase-1 (COX-1) enzyme
- Effect persists for 7-10 days
- Used for primary prophylaxis of MI, prevention of MI recurrence, and prevention of stoke in patients with history of TIA.
- Dose = 80 to 325 mg/day



Antiplatelet Drugs

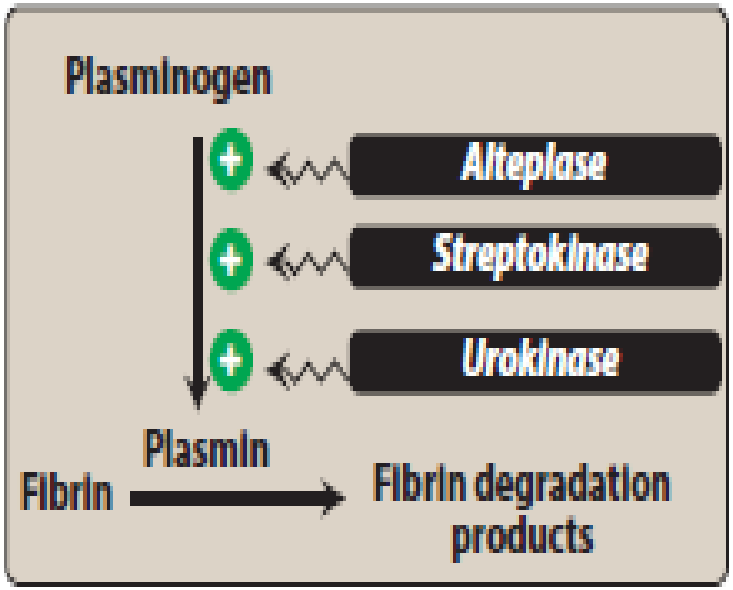
- **ADP receptor antagonists and GP IIb/IIIa receptor antagonists**





Thrombolytic Drugs

- Are used to dissolve existing thrombi
- e.g Streptokinase, Alteplase (tPA), Tenecteplase, Reteplase



Thrombolytic Drugs

Alteplase (tPA), Reteplase, Streptokinase, Tenecteplase

Preadministration Assessment:

- Therapeutic Goal:
  - To treat acute MI, massive pulmonary emboli, ischemic stroke, and DVT
- Baseline Data:
  - Obtain baseline values for BP, HR, platelet counts, hematocrit, PT, aPTT, and fibrinogen level
- Identifying High-Risk Patients:
  - *Contraindicated* for patients with active bleeding, acute pericarditis, aortic dissection, cerebral neoplasm, cerebral vascular disease, or history of intracranial bleeding.
  - *Great caution* in patients with relative contraindications – pregnancy, severe hypertension, ischemic stroke within the prior 6 months, and major surgery within the prior 2 to 4 weeks.

Thrombolytic Drugs

Alteplase (tPA), Reteplase, Streptokinase, Tenecteplase

Implementation: Administration:

- Routes: Intracoronary and IV
- Administration:
  - Depending on the drug and the specific application – IV infusion, slow IV injection, IV bolus, intracoronary infusion, or intracoronary bolus
  - *Do not administer heparin and streptokinase through the same IV line*

Ongoing Evaluation and Interventions:

- Minimizing adverse effects:
  - Hemorrhage: intracranial hemorrhage is of great concern – minimized by avoiding subQ and IM injections, minimizing invasive procedures, and minimizing concurrent use of anticoagulants and antiplatelets
  - *Severe bleeding* – stop streptokinase and give whole blood or blood products – if *bleeding continues administer aminocaproic acid*

Thrombolytic Drugs

Alteplase (tPA), Reteplase, Streptokinase, Tenecteplase

Ongoing Evaluation and Interventions:

- Minimizing adverse interactions:
  - Avoid high-dose therapy with antiplatelets or anticoagulants until thrombolytic effects have subsided.

Drugs to Treat Bleeding

Medication	Antidote for Bleeding Caused by	Adverse Effects
Aminocaproic acid *Tranexamic acid*	Fibrinolytic state	Muscle necrosis Thrombosis CVA Seizure
Protamine sulfate	*Heparin*	Flushing Nausea/vomiting Dyspnea Bradyarrhythmia Hypotension Anaphylaxis
Vitamin K1	*Warfarin*	Skin reaction Anaphylaxis

Chapter 28
Opioid Analgesics, Opioid Antagonists, and Nonopioid Centrally Acting Analgesics

Introduction

- Analgesics – drugs that relieve pain without causing loss of consciousness. ***Opioids*** are the most effective analgesics.
- Opioid – any drug, natural or synthetic, that has actions similar to those of ***morphine*** – relieving severe or chronic pain.
- Paracetamol and/or nonsteroidal anti-inflammatory drugs (NSAIDs) – relieving mild to moderate pain
- Three main opioid receptors – μ (mu), κ (kappa), and δ (delta)
- Opioid analgesics interact with mu (primarily) and kappa receptors

Introduction

- *Therapeutic use* of opioids – relief of pain (moderate to severe)
- *Adverse effects* of opioids:
  - Respiratory depression
  - Constipation
  - Orthostatic hypotension
  - Urinary retention
  - Cough suppression !!
  - Biliary colic
  - Emesis
  - Elevation of ICP
  - Euphoria/Dysphoria
  - Sedation
  - Miosis
  - Neurotoxicity

Introduction

- *Continuous opioid* use can cause ***Tolerance*** and ***Physical Dependence***.
- **Tolerance:**
  - A state at which a larger dose is required to produce the same response that could formerly be elicited by a smaller dose.
  - *Tolerance* develops to *analgesia*, *euphoria*, and *sedation*.
  - *Tolerance* also develops to *respiratory depression*.
  - *Little tolerance* develops to *constipation* and *miosis*.
  - Cross-tolerance among opioid agonists / no cross-tolerance between opioids and general CNS depressants (barbiturates, ethanol, benzodiazepines, general anesthetics)

Introduction

- *Continuous opioid* use can cause ***Tolerance*** and ***Physical Dependence***.
- **Physical Dependence:**
  - A state in which an abstinence syndrome will occur if drug use is abruptly stopped.
  - Intensity and duration of the opioid abstinence syndrome depends on half-life of the drug being used and the degree of physical dependence
  - Short half-lives opioids (e.g. morphine) has intense but brief symptoms – and vice versa with opioids with long half-lives (e.g. methadone).
  - The intensity of withdrawal symptoms parallels the degree of physical dependence.

Introduction

- **Pure Opioid Agonists:**
  - **Morphine**
  - **Codeine**
  - **Fentanyl**
  - **Methadone**
  - **Meperidine**
- **Agonist-Antagonist Opioids:**
  - **Buprenorphine**
  - **Butorphanol**
  - **Nalbuphine**
  - **Pentazocine**
- **Opioid Antagonist:**
  - **Naloxone**

Pure Opioid Agonists

Preadministration Assessment:

- Therapeutic goal:
  - Relief or prevention of moderate to severe pain
- Baseline Data:
  - Pain Assessment:
    - Assess pain before administration and 1 hour later. Determine the location, time of onset, and quality of pain.
  - Vital Signs:
    - Prior to administration, determine respiratory rate, BP, and pulse rate
- Identifying High-Risk Patients:
  - All opioids are *contraindicated* for premature infants. *Morphine* is *contraindicated* following biliary tract surgery. *Meperidine* is *contraindicated* for patients taking MAO inhibitors.

Pure Opioid Agonists

Preadministration Assessment:

- Identifying High-Risk Patients:
  - Use opioids with *caution* in patients with head injury, profound CNS depression, coma, respiratory depression, pulmonary disease (asthma), CV disease, hypotension, reduced blood volume, prostatic hypertrophy, urethral stricture, and liver impairment. *Caution* is also required when treating infants, elderly or debilitated patients, and patients receiving MAO inhibitors, CNS depressants, anticholinergic drugs, and hypotensive agents.

Implementation: Administration:

- Routes: PO, IM, IV, subQ, rectal, epidural, intrathecal, transdermal (fentanyl), and transmucosal (fentanyl).
- Dosage:
  - General guidelines:
    - Adjust dose to meet individual needs. Warn outpatients not to increase dosage without consulting the prescriber.

Pure Opioid Agonists

Implementation: Administration:

- Dosage:
  - General guidelines:
    - Oral doses are larger than parenteral doses
    - Tolerance develops – dosage escalation
    - Elderly patients generally require lower doses than younger adults
    - Neonates require relatively low doses because the BBB is poorly developed
    - Dosage should be reduced as pain subsides
  - Dosage in Patients with Cancer:
    - Opioids are used chronically
    - Cancer patients should receive opioids on a fixed schedule around-the-clock – not PRN
    - Breakthrough pain occurrence – fixed dosing should be supplemented PRN with short-acting opioid

Pure Opioid Agonists

Implementation: Administration:

- Dosage:
  - Discontinuing opioids:
    - Withdraw opioids slowly – tapering the dosage over 3 days (hospitalized patients)
    - Warn outpatients against abrupt discontinuation of treatment

Pure Opioid Agonists

Implementation: Administration:

- Administration:
  - Determine vital signs initially – withhold medication and notify prescriber if respiratory rate below 12 breaths per minute, BP is significantly below the pretreatment value, or if pulse rate is above or below the pretreatment value.
  - Opioids should be administered on a fixed schedule – with supplemental doses as needed.
  - IV injections slowly (over 4-5 minutes) – opioid antagonist and facilities for respiratory support available
  - Injections (especially IV) with patients lying down
  - Warn patients using fentanyl patches to avoid exposing the patch to direct heat (heating pad, hot tub)

Pure Opioid Agonists

Ongoing Evaluation and Interventions:

- Evaluating Therapeutic Effects:
  - Evaluate for pain control 1 hr after opioid administration.
  - If analgesia is insufficient - consult the physician about an increase in dosage.
  - Chronic patients – pain re-evaluated on a regular basis to determine dosage adequacy

- Minimizing Adverse Effects:
  - Respiratory Depression:
    - Monitor all patients – *if respiratory rate is 12 breaths per minute or less* – withhold medication and notify prescriber
    - Warn outpatients about respiratory depression – instruct them to notify prescriber if respiratory distress occur
    - Monitor closely patients who are very young, elderly, and those with respiratory disease
    - When employed during labor and delivery – respiratory depression may occur in the neonate – monitor infants closely – have naloxone available

Pure Opioid Agonists

Ongoing Evaluation and Interventions:

- Minimizing Adverse Effects:
  - Sedation:
    - Inform patients that opioids may cause drowsiness – warn them against doing hazardous activities (e.g. driving) if sedation is significant
    - Can be minimized by (1) using smaller doses given more frequently, (2) using opioids with short half-lives, and (3) giving small doses of CNS stimulants (methylphenidate or dextroamphetamine) in the morning and early afternoon

Pure Opioid Agonists

Ongoing Evaluation and Interventions:

- Minimizing Adverse Effects:
  - Orthostatic hypotension:
    - Monitor BP and pulse rate
    - Inform patients about symptoms of hypotension – advise them to sit or lie down if they occur.
    - Inform patients that hypotension can be minimized by moving slowly when assuming an erect posture.
    - Warn against walking if hypotension is significant.

Pure Opioid Agonists

Ongoing Evaluation and Interventions:

- Minimizing Adverse Effects:
  - Constipation:
    - Risk of constipation can be *reduced* by *maintaining physical activity*, *increasing intake of fiber and fluids*, and prophylactic treatment with a *stimulant laxative* (e.g. bisacodyl).
  - Urinary retention:
    - Monitor intake and output and examine the lower abdomen for bladder distension every 4 to 6 hours.
    - If there is a change in intake/output ratio, if bladder distention is detected, or if patient reports difficulty voiding – notify prescriber – catheterization may be required
    - Opioids may suppress awareness of bladder stimuli – encourage patients to void every 4 hrs.
  - Biliary colic: may be less pronounced with meperidine
  - Emesis: can be minimized by pretreatment with antiemetic (e.g. promethazine) and by having patient remain still. *Tolerance develops quickly.*

Pure Opioid Agonists

Ongoing Evaluation and Interventions:

- Minimizing Adverse Effects:
  - Cough Suppression:
    - May result in accumulation of secretions in the airways – instruct patient to cough at regular intervals
  - Miosis: impair vision in dim light – keep hospital room lighting bright during waking hours
  - Neurotoxicity: delirium, agitation, myoclonus, hyperalgesia – symptoms can be reduced with hydration, dose reduction, and opioid rotation.
- Minimizing Adverse Interactions:
  - CNS Depressants: Warn patients against use of alcohol and other depressants – risk of profound sedation and respiratory depression
  - Agonist-Antagonist Opioids: can precipitate withdrawal symptoms if administered to a patient who is physically dependent on a pure opioid agonist
  - Anticholinergic drugs: can exacerbate opioid-induced constipation and urinary retention

Pure Opioid Agonists

Ongoing Evaluation and Interventions:

- Minimizing Adverse Interactions:
  - Hypotensive drugs: can exacerbate opioid-induced orthostatic hypotension
  - Opioid antagonist: can precipitate withdrawal symptoms if administered in excessive dosage – carefully titrate the dosage of the antagonist
  - MAO inhibitors: *combination with meperidine should be avoided* – can cause delirium, hyperthermia, rigidity, convulsions, coma, and death
  - CYP3A4 inhibitors (e.g. ritonavir, ketoconazole): can increase levels of *fentanyl* – posing a risk of fatal respiratory depression – monitor patients using this combination with care

Agonist-Antagonist Opioid

Buprenorphine, Butorphanol, Nalbuphine, Pentazocine

- **Therapeutic Goal:**
  - Relief moderate to severe pain
- **Routes:**
  - PO, IV, IM, subQ, and intranasal (butorphanol)
- **Differences from Pure Opioid Agonists:**
  - Maximal pain relief – lower
  - Respiratory depression – have a ceiling / minimizing concerns about insufficient oxygenation
  - Euphoria – little
  - Should not be given to patients with acute myocardial infarction
  - Antagonist effects – withdrawal symptoms in patients physically dependent on opioid agonists

Opioid (Narcotic) Antagonist

Naloxone

- **Therapeutic Goal:**
  - Reversal of postoperative opioid effects, opioid-induced neonatal respiratory depression, and overdose with pure opioid agonist.

- **Routes:**
  - IV, IM, and subQ
  - For initial treatment administer IV

- **Dosage:**
  - Dose should be titrated carefully
  - ***Excessive doses*** may result in problems in *opioid addicts* and *postoperative patients*

Nonopioid Centrally Acting Analgesic

Tramadol

- Analogue of codeine
- Moderately strong analgesic – minimal potential for dependence, abuse, or respiratory depression.
- Weak agonist activity at mu opioid receptors + blocks uptake of NE and serotonin (activating monoaminergic spinal inhibition of pain).
- Naloxone partially blocks tramadol effects.
- Adverse effects: sedation, dizziness, headache, dry mouth, and constipation.

Chapter 26
Local Anesthetics

Introduction

- Local anesthetics – drugs that suppress pain by blocking impulse conduction along axons (sodium channels).
- Analgesia vs. Anesthesia
- Conduction is blocked only in neurons located near the site of anesthetic administration.
- It has a great advantage compared to inhalation anesthesia – no generalized depression of entire nervous system.
- Risk is lower compared to general anesthetics.

Introduction

- Two classes of local anesthetics:
  - Ester-type anesthetics (e.g. procaine, cocaine, tetracaine, benzocaine)
  - Amide-type anesthetics (e.g. lidocaine, prilocaine, articaine, bupivacaine)

- **Ester-type** anesthetics: metabolized by plasma esterases (in blood) and cause allergic reactions.
- **Amide-type** anesthetics: metabolized by hepatic enzymes and rarely cause allergic reactions.

- *Onset* of anesthesia occurs *more rapidly* with *anesthetics* that are s*mall*, *lipid soluble*, and *nonionized at physiologic pH*.

Introduction

- Termination of local anesthesia is determined by regional blood flow.
- Anesthesia is prolonged with the use of epinephrine.
- Systemic toxicity of local anesthetics include: cardiac depression, vasodilation, and CNS excitation followed by depression.
- For injected local anesthetics – an IV line should be in place prior to anesthetic administration – to permit administration of required emergency drugs.

Topical Local Anesthetics

e.g. **Lidocaine, prilocaine,** benzocaine, cocaine, dibucaine, dyclonine, pramoxine, tetracaine

Preadministration Assessment:

- Therapeutic goal:
  - Reduction of discomfort associated with local disorders of the skin and mucous membranes.
- Identifying High-Risk Patients:
  - Ester-type local anesthetics are *contraindicated* in patients with a history of serious allergic reactions.

Implementation: administration:

- Routes: Topical
- Administration:
  - Wear gloves when applying them
  - Apply in the lowest effective dose + smallest area required
  - Avoid application to injured skin

Topical Local Anesthetics

Ongoing Evaluation and Intervention:

- Minimizing Adverse Effects:
  - Systemic Toxicity:
    - Heart and CNS
    - Monitor BP, pulse rate, respiratory rate, and state of consciousness
    - Have facilities for cardiopulmonary resuscitation available
    - Systemic toxicity minimized by minimizing absorption – application to smallest area and avoid injured skin
  - Allergic reactions:
    - Allergic reactions are most likely with ester-type anesthetics
    - Avoid ester-type anesthetics in patients with a history of allergy to these drugs.

Injected Local Anesthetics

e.g. **Lidocaine, prilocaine,** procaine, bupivacaine

Preadministration Assessment:

- Therapeutic goal:
  - Production of local anesthesia for surgical, dental, and obstetric procedures.
- Identifying High-Risk Patients:
  - Ester-type local anesthetics are *contraindicated* in patients with a history of serious allergic reactions.

Injected Local Anesthetics

e.g. **Lidocaine, prilocaine,** procaine, bupivacaine

Implementation: administration:

- Preparation of the patient:
  - Nurse may be responsible to prepare the patient to receive injectable anesthetic
  - Cleansing the injection site, shaving the site when indicated, and placing the patient in a position appropriate to receive the injection
- Administration:
  - Performed by trained clinicians (physicians, dentists, nurse anesthetists)

Injected Local Anesthetics

Ongoing Evaluation and Intervention:

- Minimizing Adverse Effects:
  - Systemic Reactions:
    - Heart and CNS
    - Monitor BP, pulse rate, respiratory rate, and state of consciousness
    - Have facilities for cardiopulmonary resuscitation available
    - Manage CNS excitation with IV diazepam or IV thiopental
  - Allergic reactions:
    - Allergic reactions are most likely with ester-type anesthetics
    - Avoid ester-type anesthetics in patients with a history of allergy to these drugs
  - Labor and Delivery:
    - Can cause bradycardia and CNS depression in the newborn – monitor cardiac status – avoid concentrated (0.75%) bupivacaine

Injected Local Anesthetics

Ongoing Evaluation and Intervention:

- Minimizing Adverse Effects:
  - Self-Inflicted Injury:
    - Patients recovering from anesthesia must be protected from inadvertent harm until the anesthetic wears off
  - Spinal Headache and Urinary Retention:
    - Occurs while patients recovering from spinal anesthesia
    - Headache is posture dependent – supine position for 12 hrs would be helpful
    - Notify prescriber if patient fails to void after 8 hrs

Chapter 27
General Anesthetics

Introduction

- General anesthetics – drugs that produce unconsciousness and a lack of responsiveness to all painful stimuli.

- General anesthetics are divided into two groups: (1) inhalation anesthetics (maintenance of anesthesia) and (2) intravenous anesthetics (induction of anesthesia)

- Inhalation anesthetics – volatile liquids (**desflurane, enflurane, halothane, isoflurane, sevoflurane**) and gas (**nitrous oxide**)

- General Anesthesia vs. Local Anesthesia

Introduction

- An *ideal inhalation anesthetic* (which *does not exist*) would produce:
  - Unconsciousness / Analgesia / Muscle Relaxation / Amnesia
- Hence, a combination of drugs is used to accomplish the aforementioned effects – ***balanced anesthesia***
- These drugs include:
  - Short-acting barbiturates (e.g. thiopental) / Benzodiazepines (e.g. diazepam, lorazepam, midazolam) / Propofol / Ketamine – induction of anesthesia (IV)
  - Neuromusular blocking agents (e.g. pancuronium) – muscle relaxation
  - Opioids and nitrous oxide - analgesia

Introduction

- Inhalation anesthetics work by enhancing transmission at inhibitory synapses (GABA receptors) and by depressing transmission at excitatory synapses (NMDA receptors).
- Inhalation anesthetic potency – measured by minimum (median) alveolar concentration (MAC)
- Balanced anesthesia results in using *lower doses of general anesthetics*.
- Nitrous oxide – has very high MAC and has high analgesic potency.
- Ketamine (IV anesthetic) – produces a state known as *dissociative anesthesia* – during patient recovery, psychologic reactions occur (hallucinations, disturbing dreams, delirium)

General Anesthetics

Preoperative Patients: Counseling, Assessment, and Medicating:

- Counseling:
  - Anxiety: fear can be allayed by reassuring the patient that anesthesia will keep him or her sleep for the entire procedure, will prevent pain, and will create amnesia about the experience.
- Assessment:
  - Medication history:
    - Patient may taking drugs that affect responses to anesthetics – obtain thorough history of ALL drug use and alcohol
  - Respiratory and CV Function:
    - Most general anesthetics produce CV and respiratory depression
    - Obtain baseline values for BP, HR, and respiration

General Anesthetics

Preoperative Patients: Counseling, Assessment, and Medicating:

- Preoperative Medication:
  - e.g. benzodiazepines, opioids, anticholinergic agents – administered by nurse 30-60 minutes before surgery
  - Needed to calm patient, provide analgesia, and counteract adverse effects of general anesthesia

General Anesthetics

Postoperative Patients: Ongoing Evaluation and Interventions:

- Evaluations and Interventions – Specific organ Systems:
  - CV and Respiratory Systems:
    - Anesthetics depress CV and respiratory function
    - Determine BP, pulse rate, and respiration immediately upon receipt of the patient – repeat monitoring at brief intervals until recovery is complete
    - Have facilities for respiratory support available
  - CNS
    - Precautions are needed until return of CNS function – complete recovery from anesthesia
    - Employ side rails or straps to avoid accidental falls
    - Exercise discretion in conversation during early stage of emergence

General Anesthetics

Postoperative Patients: Ongoing Evaluation and Interventions:

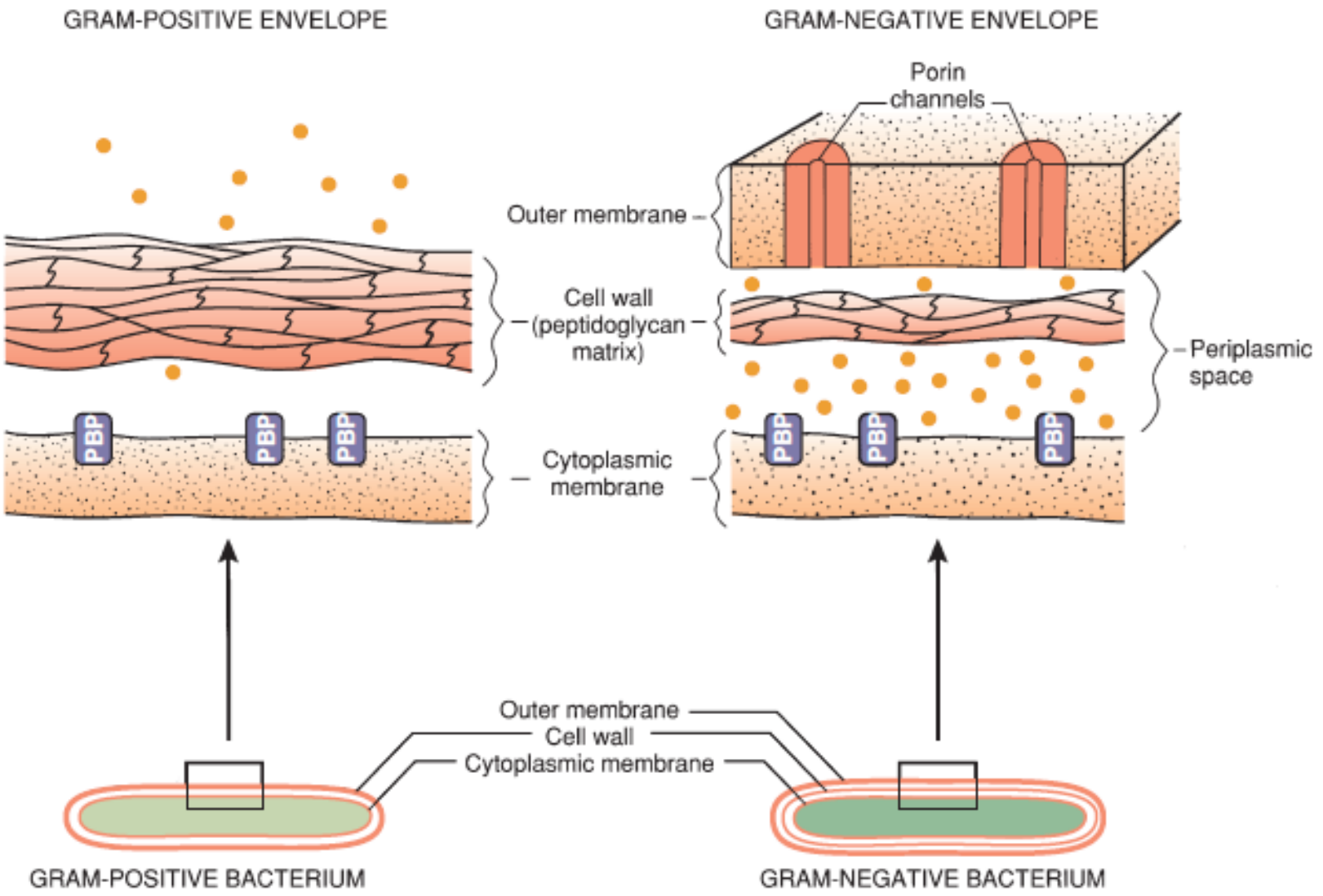
- Evaluations and Interventions – Specific organ Systems:
  - GI Tract:
    - Bowel function may be compromised by surgery or drugs employed adjunct to anesthesia – muscarinic agonist may be needed to restore peristalsis
    - Emesis is potential postanesthetic reaction – antiemetic may be needed / head position as well
  - Urinary Tract
    - Anesthetics can decrease urine production by reducing renal blood flow – monitor urine output
    - Catheterization or medication may be needed

General Anesthetics

Postoperative Patients: Ongoing Evaluation and Interventions:

- Management of postoperative pain:
  - As anesthesia wears off – patient may experience postoperative pain
  - Opioid may be required
  - However, caution is needed as opioids may cause respiratory depression – this will be added to residual respiratory depression from anesthesia
  - Balance – relieve pain and maintaining ventilation

Chapter 84
Drugs That Weaken the Bacterial Cell Wall I: Penicillins


GRAM-POSITIVE ENVELOPE
GRAM-NEGATIVE ENVELOPE
Porin channels
Outer membrane
Cell wall (peptidoglycan matrix)
Periplasmic space
Cytoplasmic membrane
PBP
PBP
PBP
PBP
PBP
PBP
Outer membrane
Cell wall
Cytoplasmic membrane
GRAM-POSITIVE BACTERIUM
GRAM-NEGATIVE BACTERIUM

Introduction

- Examples of **Penicillins**
  - Amoxicillin
  - **Amoxicillin/clavulanate**
  - Ampicillin
  - **Ampicillin/sulbactam**
  - Dicloxacillin
  - Nafcillin
  - Oxacillin
  - Penicillin G
  - Penicillin V
  - Piperacillin
  - **Piperacillin/tazobactam**

Introduction

- Penicillins weaken the bacterial cell wall, causing lysis and death.
- Some bacteria resist penicillins by producing penicillinases (beta-lactamases) – beta-lactamase inhibitors are used.
- Gram-negative bacteria are resistant to penicillins that cannot penetrate the gram-negative cell envelope.
- The principal adverse effect of penicillins is allergic reaction.
- Patients allergic to one penicillin should be considered cross-allergic to all other penicillins. In addition, they have about a 1% chance of cross-allergy to cephalosporins.
- Vancomycin, erythromycin, and clindamycin are safe and effective alternatives to penicillins for patients with penicillin allergy.

Introduction

- Penicillins are normally eliminated rapidly by the kidneys.
- The principal differences among the penicillins relate to antibacterial spectrum, stability in stomach acid, and duration of action.
- Penicillin G has a narrow antibacterial spectrum and is unstable in stomach acid.
- Benzathine penicillin G is released very slowly- IM injection.
- Broad-spectrum penicillins, such as ampicillin and amoxicillin, have useful activity against gram-negative bacilli.
- Beta-lactamase inhibitors are combined with certain penicillins to increase their activity.
- Penicillins should not be combined with aminoglycosides (e.g., gentamicin) in the same IV solution.

Penicillins

Preadministration Assessment:

- Therapeutic goal:
  - Treatment of infections caused by sensitive bacteria.
- Baseline data:
  - Samples for microbiologic cultures + skin test for patients with history of penicillin allergy.
- Identifying High-Risk Patients:
  - Penicillins should be used with *extreme caution*, in patients with a *history* of *severe allergic reactions* to penicillins, cephalosporins, or carbapenems.

Implementation: administration:

- Routes: Oral, IV, IM
- Dosage:
  - For penicillin G are prescribed in units (1 unit equals 0.6 mg).
  - All other penicillins are prescribed in *mg* or *g*.

Penicillins

Implementation: administration:

- Administration:
  - During IM injection - **aspirate**.
  - Take care to avoid injection into a nerve.
  - Instruct the patient to take oral penicillins with a full glass of water 1 hour before meals or 2 hours after. Penicillin V, amoxicillin, and amoxicillin/clavulanate may be taken with meals.
  - Instruct the patient to complete the prescribed course of treatment, even though symptoms may abate before the full course is over.

Penicillins

Ongoing Evaluation and Intervention:

- Evaluating Therapeutic Effects
  - Monitor of antimicrobial effects
- Monitoring Kidney Function
  - Measuring intake and output / Notify the prescriber if a significant change in intake/output ratio develops.
- Minimizing Adverse Effects:
  - Allergic reactions: (common / rarely – anaphylaxis)
    - For patients with prior allergic responses, a skin test may be ordered – when skin tests are performed, epinephrine and facilities for respiratory support should be immediately available.
    - Advise patients with penicillin allergy to wear some form of identification (e.g., Medic Alert bracelet) to alert emergency healthcare personnel.
    - Instruct outpatients to report any signs of an allergic response.

Penicillins

Ongoing Evaluation and Intervention:

- Minimizing Adverse Effects:
  - Allergic reactions:
    - Whenever a parenteral penicillin is used, keep the patient under observation for at least 30 minutes. If anaphylaxis occurs, treatment consists of epinephrine (subQ, IM, or IV) plus respiratory support.
    - As a rule – patients with history of penicillin allergy should not receive penecillins.
    - If allergy was mild – oral cephalosporins may be used
    - If severe immediate allergy with cephalosporins occurred – stopped
  - **Sodium Loading** (High IV doses of sodium penicillin G) + **Hyperkalemia** (High doses of IV potassium penicillin G) - Monitor electrolytes and cardiac status.
  - Take care to avoid intra-arterial injection or injection into peripheral nerves because serious injury can result.

Chapter 85
Drugs That Weaken the Bacterial Cell Wall II: Cephalosporins, Carbapenems, Vancomycin, Telavancin, Aztreonam, and Fosfomycin

Introduction

- Examples of **Cephalosporins**
  - Cefaclor
  - Cefadroxil
  - Cefazolin
  - Cefdinir
  - Cefditoren
  - Cefepime
  - Cefixime
  - Cefotaxime
  - Cefotetan
  - Cefoxitin
  - Cefpodoxime
  - Cefprozil
  - Ceftaroline
  - Ceftazidime
  - Ceftibuten
  - Ceftriaxone
  - Cefuroxime
  - Cephalexin

Introduction

- Cephalosporins are beta-lactam antibiotics that weaken the bacterial cell wall, causing lysis and death.
- Resistance - beta-lactamases.
- Five "generations" – In general, as we progress from first- to fifth-generation drugs, there is (1) increasing activity against gram-negative bacteria, (2) increasing resistance to destruction by beta-lactamases, and (3) increasing ability to reach the CSF.
- Eliminated by kidneys (except for ceftriaxone) – renal impairments
- Causes allergy – 1% cross-reactivity with patients allergic to penicillins
- Cefotetan and ceftriaxone - can cause bleeding tendencies.

Introduction

- Imipenem (beta-lactam antibiotic) – broad spectrum of action among all other antimicrobial drugs (parenterally)
- Vancomycin is an important but potentially toxic drug used primarily for (1) Clostridium difficile infection, (2) MRSA infection, and (3) serious infections by susceptible organisms in patients allergic to penicillins.
- The principal toxicity of vancomycin is renal failure.

Cephalosporins

Preadministration Assessment:

- Therapeutic goal:
  - Treatment of infections caused by sensitive bacteria.
- Baseline data:
  - Samples for microbiologic cultures.
- Identifying High-Risk Patients:
  - *Contraindicated* for patients with a history of allergic reactions to cephalosporins or of severe allergic reactions to penicillins.
  - *Ceftriaxone* is contraindicated for neonates who are receiving (or expected to receive) IV calcium.

Implementation: administration:

- Routes: Oral, IV, IM
- Dosage:
  - Reduction in patients with renal impairment (except ceftriaxone)

Cephalosporins

Implementation: administration:

- Administration:
  - Oral
    - Advise patients to take oral cephalosporins with food if gastric upset occurs.
    - Instruct patients to refrigerate oral suspensions.
    - Instruct patients to complete the prescribed course of therapy even though symptoms may abate before the full course is over.
  - Intramuscular - Make IM injections deep into a large muscle. Intramuscular injections are frequently painful; forewarn the patient. Check the injection site for induration, tenderness, and redness—and notify the prescriber if these occur.
  - Intravenous - Techniques for IV administration are bolus injection, slow injection (over 3 to 5 minutes), and continuous infusion. The prescriber's order should specify which method to use; request clarification if the order is unclear.

Cephalosporins

Ongoing Evaluation and Intervention:

- Evaluating Therapeutic Effects
  - Monitor of antimicrobial effects
- Minimizing Adverse Effects:
  - Allergic reactions:
    - Hypersensitivity reactions are common
    - Rarely, life-threatning anaphylaxis occur – administer parenteral epinephrine and provide respiratory support
    - Instruct patient to report any sign of allergy.
  - Bleeding:
    - *Cefotetan* and *ceftriaxone* – promote bleeding – if occurred, discontinue drug
    - Monitor prothrombin time, bleeding time, or both / observe patients for signs of bleeding
    - Parenteral vitamin K can correct abnormal bleeding

Cephalosporins

Ongoing Evaluation and Intervention:

- Minimizing Adverse Effects:
  - Bleeding:
    - Caution in patients with history of bleeding disorders or receiving drugs that interfere with hemostasis
  - Thrombophlebitis: IV formulations – minimized by rotating injection site and inject cephalosporins slowly and in dilute solution
  - Hemolytic Anemia - if developed – cephalosporins discontinued and blood transfusions may be given as needed.
  - Clostridium difficile Infection (CDI):
    - All cephalosporins (especially broad-spectrum) can promote CDI - diarrhea and pseudomembranous colitis.
    - If CDI is diagnosed - discontinue the cephalosporin.
    - Treat with metronidazole or vancomycin

Cephalosporins

Ongoing Evaluation and Intervention:

- Minimizing Adverse Interactions:
  - Alcohol
    - Cefazolin and cefotetan can cause alcohol intolerance - disulfiram-like reaction may occur if alcohol is consumed - warn patients not to drink alcoholic beverages.
  - Drugs That Promote Bleeding
    - Avoid combinations with cefotetan and ceftriaxone.
  - Calcium and Ceftriaxone – as discussed before

Chapter 86
Bacteriostatic Inhibitors of Protein Synthesis: Tetracyclines, Macrolides, and Others

Introduction

- Examples of **Tetracyclines**
  - Demeclocycline
  - **Doxycycline**
  - Minocycline
  - Tetracycline

- Examples of **Macrolides**
  - Erythromycin
  - Clarithromycin
  - **Azithromycin**

Introduction

- Tetracyclines are broad-spectrum, bacteriostatic antibiotics that inhibit bacterial protein synthesis.
- Tetracyclines are first-choice drugs for just a few infections, such as those caused *Chlamydia trachomatis*, *H. pylori* (i.e., peptic ulcer disease), *B. anthracis* (anthrax), and *M. pneumoniae*.
- Tetracyclines form insoluble chelates with cations (Ca, Fe, Mg, Al, Zn) – not administered with calcium supplements, milk products, iron supplements, magnesium-containing laxatives, and most antacids.
- Tetracycline, demeclocycline, and doxycycline - on an empty stomach. / Minocycline – with meals

Introduction

- Tetracycline and demeclocycline should not be given to patients with renal failure --- **doxycycline**
- Tetracyclines can stain developing teeth - not be given to pregnant women and breast-feeding women or children under 8 years old.
- Tetracyclines can cause superinfections, especially *C. difficile*–associated diarrhea (CDAD) and overgrowth of the mouth, pharynx, vagina, or bowel with *Candida albicans*.
- Erythromycin, the prototype of the macrolide antibiotics, is a bacteriostatic drug that inhibits bacterial protein synthesis.
- Erythromycin has an antimicrobial spectrum similar to that of penicillin G, and hence can be used in place of penicillin G in patients with penicillin allergy.

Tetracyclines

Preadministration Assessment:

- Therapeutic goal:
  - Treatment of tetracycline-sensitive infections, acne, and periodontal disease.
- Baseline data:
  - Samples for microbiologic cultures.
- Identifying High-Risk Patients:
  - They are *contraindicated* in pregnant women and in children younger than 8 years, and should be avoided in women who are breast-feeding.
  - Tetracycline and demeclocycline must be used with great caution in patients with significant renal impairment.

Implementation: administration:

- Routes: Oral, parenteral

Tetracyclines

Implementation: administration:

- Administration:
  - Oral
    - Advise patients to take most oral tetracyclines on an empty stomach and with a full glass of water. Minocycline – may taken with food.
    - Instruct patients – at least 2 hours between ingestion of tetracyclines and ingestion of chelators.
    - Instruct patients to complete the prescribed course
  - Parenteral
    - Only when oral administration is ineffective or cannot be tolerated

Tetracyclines

Ongoing Evaluation and Intervention:

- Minimizing Adverse Effects:
  - Gastrointestinal Irritation:
    - Inform patients that GI distress can be reduced by taking tetracyclines with meals, although absorption may be reduced.
  - Effect on teeth:
    - Discolor developing teeth – contraindicated as discussed before
  - Superinfection:
    - Promote bacterial infection in bowel – diarrhea – patient notify prescriber
    - If superinfection is diagnosed - discontinue tetracyclines immediately. Treatment of *C. difficile*–associated diarrhea (CDAD) = oral vancomycin or metronidazole, plus fluid and electrolyte replacement.

Tetracyclines

Ongoing Evaluation and Intervention:

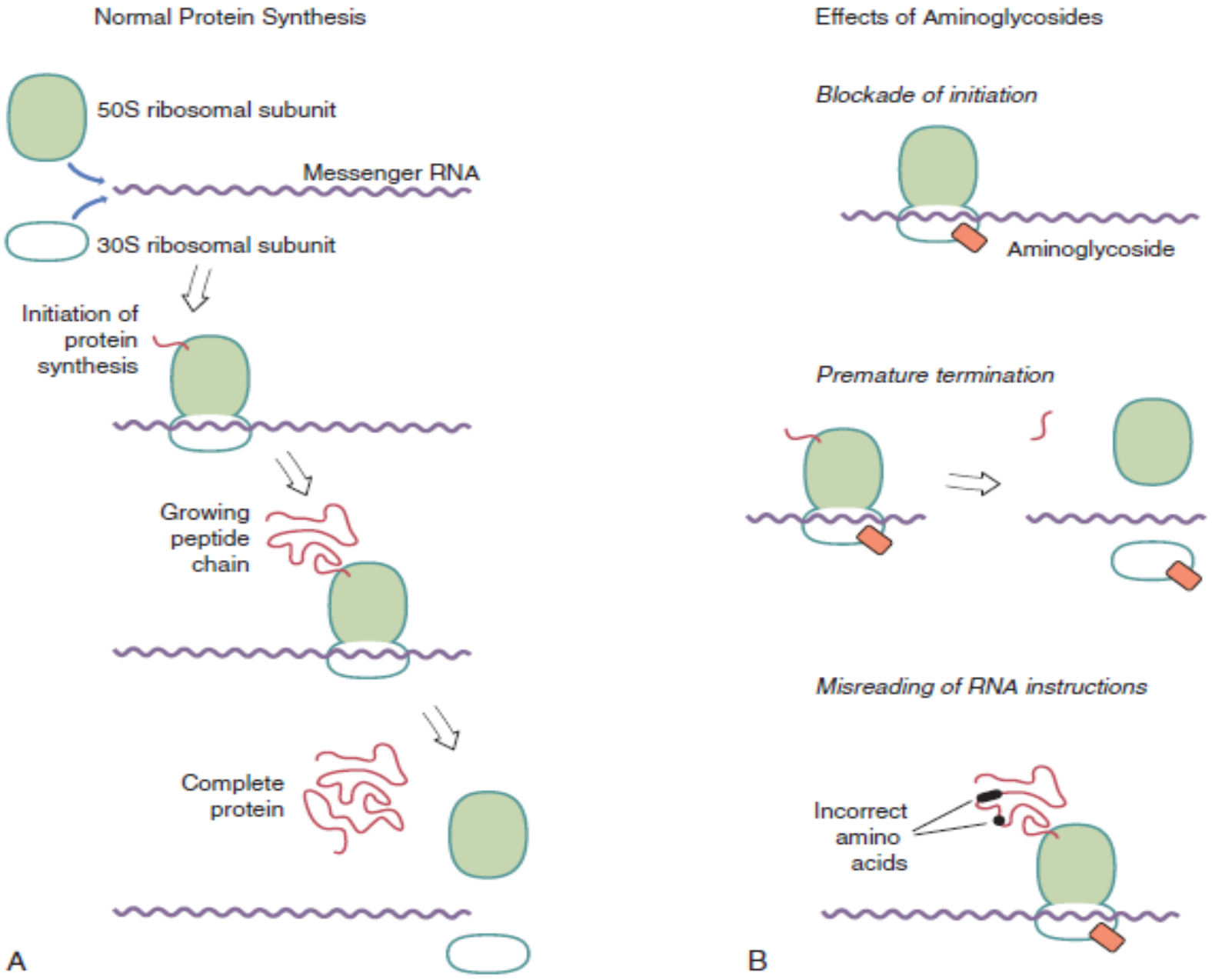
- Minimizing Adverse Effects:
  - Superinfection:
    - Fungal overgrowth may occur in the mouth, pharynx, vagina, and bowel – treated by discontinuing the drug or by antifungal drug
    - Inform patients about symptoms of fungal infection and advise them to notify the prescriber if these occur
  - Hepatotoxicity:
    - Can cause fatty infiltration of the liver – jaundice – risk can be reduced by avoiding high-dose IV therapy and by withholding tetracyclines from pregnant and postpartum women who have kidney disease
  - Renal toxicity:
    - Can exacerbate pre-existing renal impairment / tetracycline + demeclocycline should not be used in patients with kidney disease

Tetracyclines

Ongoing Evaluation and Intervention:

- Minimizing Adverse Effects:
  - Photosensitivity:
    - They can increase the sensitivity of the skin to UV light – increased risk of sunburn.
    - Advise patients to avoid prolonged exposure to sunlight, wear protective clothing, and apply a sunscreen to exposed skin.

Chapter 87
Aminoglycosides: Bactericidal Inhibitors of Protein Synthesis


Normal Protein Synthesis
50S ribosomal subunit
Messenger RNA
30S ribosomal subunit
Initiation of protein synthesis
Growing peptide chain
Complete protein
A
Effects of Aminoglycosides
Blockade of initiation
Aminoglycoside
Premature termination
Misreading of RNA instructions
Incorrect amino acids
B

Introduction

- Examples of **Aminoglycosides**
  - Amikacin
  - Gentamicin
  - Kanamycin
  - Neomycin
  - Paromomycin
  - Streptomycin
  - Tobramycin

Introduction

- Aminoglycosides are antibiotics used primarily against aerobic gram-negative bacilli.
- Aminoglycosides disrupt protein synthesis and cause rapid bacterial death.
- Aminoglycosides are highly polar polycations - not absorbed from the GI tract / do not cross BBB / excreted rapidly by the kidneys.
- Aminoglycosides can cause irreversible injury to sensory
- cells of the inner ears - hearing loss and disturbed balance.
- Aminoglycosides are nephrotoxic - reversible.

Aminoglycosides

Preadministration Assessment:

- Therapeutic goal:
  - Parenteral Therapy: Treatment of serious infections caused by gram-negative aerobic bacilli. Gentamicin in combination with vancomycin or a beta-lactam antibiotic - to treat serious infections caused by certain gram-positive bacteria.
  - Oral Therapy: Suppression of bowel flora before elective colorectal surgery.
  - Topical Therapy: Treatment of local infections of the eyes, ears, and skin.
- Identifying High-Risk Patients:
  - Aminoglycosides must be used with caution in patients with renal impairment, pre-existing hearing impairment, and myasthenia gravis, and in patients receiving ototoxic drugs (especially ethacrynic acid), nephrotoxic drugs (e.g., amphotericin B, cephalosporins, vancomycin, cyclosporine, NSAIDs), and neuromuscular blocking agents.

Aminoglycosides

Implementation: administration:

- Routes:
  - IM and IV: Gentamicin, tobramycin, amikacin, kanamycin.
  - Oral: Neomycin, paromomycin.
  - Topical: Gentamicin, neomycin, tobramycin.
- Dosing Schedule:
  - Parenteral - one large dose each day or in two or three divided doses
- Administration
  - Parenterally (IV, IM) to treat systemic infections. IV infusions should be done slowly (over 30 minutes or more).
  - Do not mix aminoglycosides and penicillins in the same IV solution.
  - In patients with renal impairment, the dosage should be reduced or the dosing interval increased.

Aminoglycosides

Ongoing Evaluation and Intervention:

- Monitoring Summary
  - Monitor aminoglycoside levels (peaks and troughs), inner ear function (hearing and balance), and kidney function (creatinine clearance, BUN, and urine output).
- Minimizing Adverse Effects:
  - Ototoxicity:
    - Can damage the inner ears, causing irreversible impairment of hearing and balance
    - Instruct patients to report symptoms of ototoxicity
    - Ototoxicity detected – aminoglycosides withdrawn
  - Nephrotoxicity
    - Can cause acute tubular necrosis, which is usually reversible
    - If oliguria or anuria develops - withhold the aminoglycoside and notify the prescriber.

Aminoglycosides

Ongoing Evaluation and Intervention:

- Minimizing Adverse Effects:
  - Neuromuscular Blockade:
    - They can inhibit neuromuscular transmission – causing potentially fatal respiratory depression.
    - Carefully observe patients with myasthenia gravis and patients receiving skeletal muscle relaxants or general anesthetics.
    - Reversed with IV calcium gluconate.

- Minimizing Adverse Interactions:
  - Penicillins
  - Ototoxic and Nephrotoxic Drugs
  - Skeletal Muscle Relaxants